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# **UVULOPALATOPHARYNGOPLASTY: PATIENT SELECTION, LONG-TERM OUTCOMES, AND SIDE EFFECTS**

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# Uvulopalatopharyngoplasty: Patient Selection, Long-Term Outcomes, and Side Effects

## THESIS FOR DOCTORAL DEGREE (PhD)

This thesis will be publicly defended in lecture hall B64, at Karolinska University Hospital, Huddinge, Friday, 13 November, 9:00 am.

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To Tuss, Udd and Leo



## ABSTRACT

Uvulopalatopharyngoplasty (UPPP) is the most common surgical treatment for adult patients with obstructive sleep apnea (OSA). Its short-term efficacy, as measured through polysomnography, is well-established and has been demonstrated in two randomized controlled trials in recent years. However, less is known about subjective sleep quality, long-term efficacy, and side effects after surgery. In addition, the reliability of the most widespread clinical test for selecting patients for surgery—the Friedman staging system—is unclear.

The Friedman staging system uses a combination of tonsil size and tongue position to predict the likelihood of successful surgery. The objective of **studies I and II** was to evaluate the staging system by determining its inter-examiner agreement. In **study I**, 15 doctors evaluated the system by using it on each other. In **study II**, 14 doctors evaluated the system by using it on 12 patients with OSA. Cohen's kappa analysis was used. Kappa values of 1 represents perfect agreement, and values of 0 represent no more agreement than would have been expected through random chance. In **study I**, the median kappa was 0.36 for tongue position. In **study II**, the median kappa was 0.32 for tongue position, 0.62 for tonsil size, and 0.38 for the Friedman staging system. These findings correspond to poor agreement, indicating that the system is an uncertain method for selecting patients for UPPP.

Uvulopalatopharyngoplasty was first described in the eighties. Since then, there has been several modifications. The modified UPPP used in this thesis includes a tonsillectomy and is performed with cold instruments. It is less radical to the palate compared to the original procedure.

The objective of **study III** was to investigate whether modified UPPP improves sleep quality by using the Functional Outcomes of Sleep Questionnaire and the Karolinska Sleep Questionnaire. The study consisted of two parts: Part 1 was a randomized controlled trial with two study groups (intervention and controls), and Part 2 was a post-operative follow-up of all patients (intervention and controls who received delayed surgery) with an analysis of outcomes at six and 24 months after UPPP. In eight out of nine subscales, there were significant improvements between the intervention and controls in favor of UPPP. In addition, at the six- and 24-month post-operative follow-ups of all patients, eight out of nine subscales were significantly improved compared to the baseline. These findings suggest a real and lasting beneficial effect of UPPP on subjective sleep quality, although a placebo effect cannot be excluded.

Previous studies have demonstrated high rates of side effects following pharyngeal surgery. The objective of **study IV** was to evaluate side effects and satisfaction with modified UPPP after six and 24 months. In addition, patients who reported side effects or regretted having surgery at the follow-up were contacted for an individual telephone interview approximately nine years after surgery. In our sample, the majority of patients were satisfied 24 months after surgery, despite one third experiencing side effects. Younger patients had fewer side effects than older patients. After nine years, the side effects were mostly of minor concern.

Studies on the long-term effects of UPPP are few in number, often include small study samples, and use different outcome measures and surgical techniques. The objective of **study V** was to investigate whether modified UPPP remained effective after eight years using polysomnography and questionnaires. In addition, the study investigated whether certain baseline factors could predict long-term outcomes. The results indicated that modified UPPP had a significant positive effect as a long-term treatment for OSA, although the effect on apnea-hypopnea index also significantly decreased over time. Daytime sleepiness, on the other hand, appeared to remain improved even in the long term. High body mass index at baseline and an increase in body mass index predicted reduced long-term outcomes.



## POPULÄRVETENSKAPLIG SAMMANFATTNING

Snarkning kan vara allt från ett harmlöst ljud till en allvarlig sjukdom med andningsuppehåll och ökad dödlighet. Det senare som följd av obstruktiv sömnapné – ett tillstånd med återkommande andningsstopp under sömn. Sjukdomen orsakas av att muskulatur och vävnad i svalget under sömn faller ihop och täpper till luftvägen. Tillståndet, som blir allt vanligare, drabbar ungefär 10% av befolkningen. För att veta om man har obstruktiv sömnapné (OSA) behöver man göra en polysomnografi, det vill säga en nattlig andningsregistrering. En polysomnografi mäter antalet andningsuppehåll under natten och är gyllene standard för diagnostik av OSA. Mer än 30 andningsuppehåll per timme räknas som grav sömnapné, vilket medför ökad risk för hjärtinfarkt, stroke och trafikolyckor.

Den mest effektiva behandlingen mot sömnapné är CPAP (Continuous Positive Airway Pressure). CPAP ger en luftström med ett övertryck som gör att luftvägen hålls öppen. En annan effektiv behandling är en apnébettskena. Många patienter tolererar dock varken sin apnébettskena eller CPAP och har därför ingen behandling alls. För dessa patienter kan svalgplastik med borttagande av halsmandlarna (uvulopalatopharyngoplastik) vara ett alternativ.

Det har visat sig svårt att välja ut lämpliga patienter för svalgplastik. En mycket använd metod är Friedmans graderingssystem. Friedmans graderingssystem väger samman storleken på halsmandlarna med tungans position i munnen. Patienter med stora halsmandlar och en lågt sittande tunga har 80% effekt mot andningsuppehållen, medan motsvarande siffra för patienter med små halsmandlar, men en högt sittande tunga, bara är 10%. Problemet med Friedmans graderingssystem är att det kan vara subjektivt. Det vill säga att olika kirurger graderar sina patienter olika. I **studie I** och i **studie II** utvärderades metoden, och det visade sig att kirurgernas gradering skilde sig mycket åt. Metoden bör därför användas med försiktighet.

Vår forskningsgrupp har tidigare genomfört en randomiserad kontrollerad studie på 65 patienter med måttlig till allvarlig OSA. Den visade att operation minskade antalet nattliga andningsuppehåll och gjorde patienterna piggare på dagarna och med ökad livskvalitet. I **studie III** undersöktes detta ytterligare. Studien var uppdelad i två delar; en randomiserad kontrollerad studie där hälften av patienterna opererades direkt och hälften fick vänta på operation (kontrollgrupp). Alla följdes upp efter sex månader med en ny polysomnografi och med nya enkäter. Patienter som opererats förbättrades signifikant, medan kontrollgruppen inte gjorde det. Sedan opererades även kontrollgruppen, som då också förbättrades. Efter två år undersöktes hela gruppen igen och man kunde se att förbättringen hade hållit i sig. En invändning vid alla behandlingar, och i synnerhet

enkätundersökningar, är att resultaten skulle kunna vara en placebo-effekt. I den aktuella studien fanns signifikanta samband mellan förbättring av symtom och minskning av objektivet registrerade andningsuppehåll, och effekten kvarstod även över två år. Det talar emot en placebo-effekt, även om det inte kan uteslutas.

En del studier har visat på en hög grad av biverkningar efter svalgplastik. Det finns dock olika varianter på svalgplastik som är mer eller mindre kirurgiskt omfattande. Man kan till exempel använda kall (icke-elektriska instrument) eller varm teknik (elektriska instrument, till exempel laser eller coblation). Det försvårar bedömningen av hur mycket biverkningar som verkligen finns. I **studie IV** undersöks graden av biverkningar och nöjdhet efter operation i den variant av konservativ svalgplastik med kalla verktyg som används sedan 2007 på Karolinska, så kallad modifierad svalgplastik med tonsillektomi. Studien visade att en majoritet av patienterna (ca 90%) var nöjda med operationen efter sex månader och fortsatte att vara nöjda efter två år. Ungefär en tredjedel av patienterna rapporterade dock biverkningar av något slag. De blev kontaktade över telefon efter nio år. Biverkningarna fanns då kvar hos mer än hälften av dem, men upplevdes som milda och inte särskilt besvärande.

Långtidseffekten efter svalgplastik är bara delvis studerad sedan tidigare. De flesta studier har visat att effekten av operation avtar över tid. Men det är svårt att dra någon slutsats då studierna har tittat på olika operationsmetoder och med olika lång uppföljningstid. Syftet med **studie V** var att undersöka långtidseffekten (åtta år) av svalgplastik med polysomnografi och med en enkät som mäter dagsömnighet. Studien visade att operation var effektivt även på lång sikt, men att effekten på antal andningsuppehåll delvis avtar. Patienter som var överviktiga från början och som dessutom ökade sin vikt hade ett sämre långtidsresultat. Den subjektiva förbättringen i dagsömnighet avtog dock inte, utan höll sig stabil från operationen och till uppföljningen efter åtta år.

## LIST OF SCIENTIFIC PAPERS

- I. **Sundman J**, Bring J, Friberg D. Poor inter-examiner agreement on Friedman tongue position. *Acta Oto-Laryngologica*. 2017;137(5):554–6.
- II. **Sundman J**, Fehrm J, Friberg D. Low inter-examiner agreement of the Friedman staging system indicating limited value in patient selection. *Eur Arch Oto-Rhino-Laryngology*. 2018;275(6):1541–5.
- III. **Sundman J**, Friberg D, Bring J, Lowden A, Nagai R, Browaldh N. Sleep Quality After Modified Uvulopalatopharyngoplasty: Results From the SKUP3 Randomized Controlled Trial. *Sleep*. 2018;41(11).
- IV. Friberg D, **Sundman J**, Browaldh N. Long-term evaluation of satisfaction and side effects after modified uvulopalatopharyngoplasty. *Laryngoscope*. 2020;130(1):263–8.
- V. **Sundman J**, Browaldh N, Fehrm J, Friberg D. Eight-year Follow-up of Modified Uvulopalatopharyngoplasty in Patients with Obstructive Sleep Apnea. *Laryngoscope*. 2020, 24 July. doi:10.1002/lary.28960

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## LIST OF ABBREVIATIONS

AASM	American Academy of Sleep Medicine
AHI	Apnea-hypopnea index
BMI	Body mass index
CI	Confidence interval
CPAP	Continuous positive airway pressure
DISE	Drug-induced sleep endoscopy
ENT	Ear, nose, and throat
ESS	Epworth Sleepiness Scale
FOSQ	Functional Outcome of Sleep Questionnaire
ICSD	International Classification of Sleep Disorders
ITT	Intention-to-treat
KSQ	Karolinska Sleepiness Questionnaire
MRD	Mandibular retaining device
OCST	Out-of-center sleep testing
ODI	Oxygen desaturation index
OSA	Obstructive sleep apnea
PG	Polygraphy
PSG	Polysomnography
RCT	Randomized controlled trial
RDI	Respiratory distress index
RERA	Respiratory effort-related arousal
SD	Standard deviation
SKUP3	Sleep apnea Karolinska UPPP
TE	Tonsillectomy
UPPP	Uvulopalatopharyngoplasty





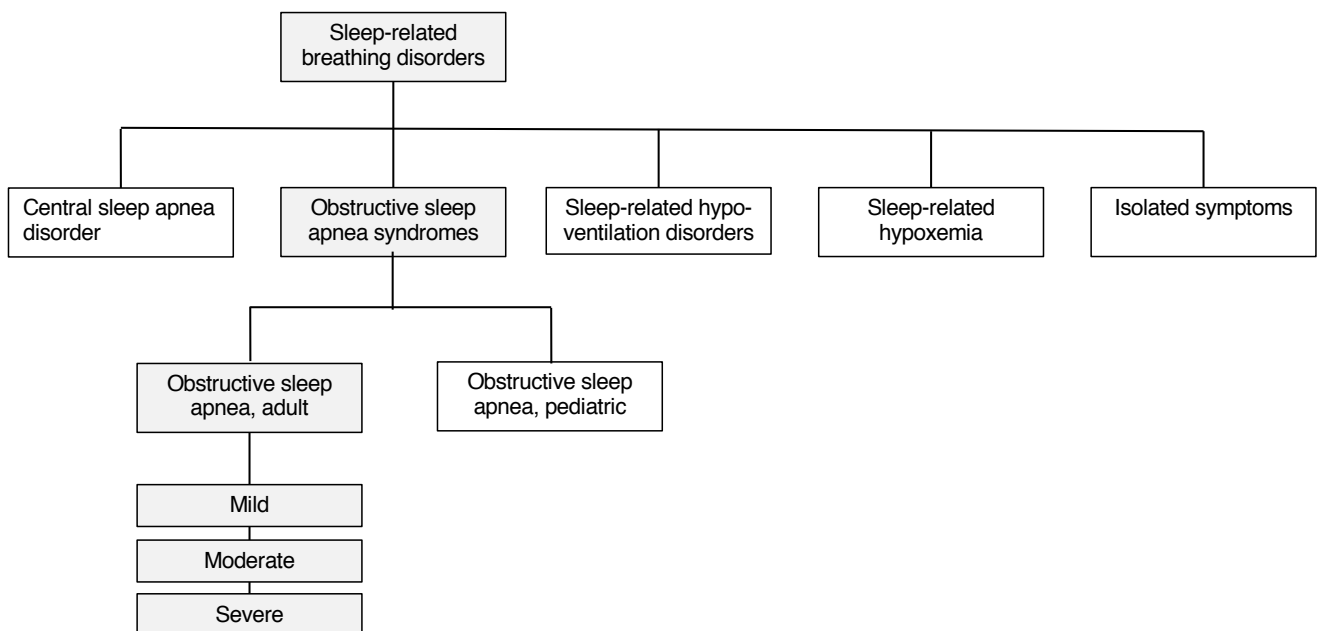


# 1 INTRODUCTION

## 1.1 BACKGROUND

### 1.1.1 Definitions

Sleep-related breathing disorders are one of six categories of sleep disorders defined in the third edition of the International Classification of Sleep Disorders (ICSD)<sup>1</sup> published by the American Academy of Sleep Medicine (AASM) in 2014. Sleep-related breathing disorders are further divided into five subgroups, all of which are characterized by impaired respiration during sleep and include a range of conditions: central sleep apnea, obstructive sleep apnea (OSA), sleep-related hypoxemia, sleep-related hypoventilation disorders, and isolated symptoms and normal variants, as shown in Figure 1. It is common for several of these conditions to be present in the same patient. For example, central and obstructive sleep apnea are frequently encountered in combination. Furthermore, since OSA occurs in both the adult and pediatric population, a final division is made between these two groups. Lastly, OSA is graded according to severity as mild, moderate, or severe, as discussed in detail later in the thesis.



**Figure 1.** Overview of sleep-related breathing disorders. Adapted from the International Classification of Sleep Disorders - Third Edition

### 1.1.2 Criteria for diagnosis

According to the ICSD, criteria for the diagnosis of OSA can be symptoms (e.g. snoring, sleepiness, fatigue, insomnia, observed apnea, or subjective respiratory disturbance) or a related disorder (e.g. hypertension, atrial fibrillation, diabetes, coronary artery disease, stroke, congestive heart failure, cognitive dysfunction, or mood disorder) in combination with five or more obstructive respiratory events (e.g. obstructive apneas, hypopneas, or respiratory effort related arousals) per hour of sleep measured with polysomnography (PSG). Obstructive respiratory events of more than 15 per hour also meets the criteria, even without evidence of symptoms or associated disorders.<sup>2</sup> The diagnostic criteria are summarized in Table 1.

**Table 1.** Diagnostic criteria for obstructive sleep apnea, adult (adapted from ICSD-3)

(A and B) or C satisfy the criteria.	
A. The presence of one or more of the following:	
1. The patient complains of sleepiness, non-restorative sleep, fatigue, or insomnia symptoms.	
2. The patient wakes with breath-holding, gasping, or choking.	
3. The bed partner or other observer reports habitual snoring, breathing interruptions, or both during the patient's sleep.	
4. The patient has been diagnosed with hypertension, a mood disorder, cognitive dysfunction, coronary artery disease, stroke, congestive heart failure, atrial fibrillation, or type 2 diabetes mellitus.	
B. PSG (or OCST) demonstrates:	
Five or more predominantly obstructive respiratory events (obstructive and mixed apneas, hypopneas or RERA) per hour of sleep (PSG) or hour of monitoring (OCST)	
Or	
C. PSG (or OCST) demonstrates:	
Fifteen or more predominantly obstructive respiratory events (apneas, hypopneas or RERA) per hour of sleep (PSG) or hour of monitoring (OCST)	
<i>Note.</i> "PSG" refers to polysomnography, "OCST" refers to out-of-center sleep testing or polygraphy and "RERA" refers to respiratory effort-related arousals.	

It is noteworthy that the criteria for a diagnosis of OSA is fulfilled with obstructive respiratory events of only five, in combination with, for example, common disorders such as depression or hypertension. This is new compared to the second edition of ICSD (ICSD-2) from 2005. Another significant change from the previous edition is that a respiratory index can be obtained from an out-of-center sleep testing or ambulant polygraphy (PG). The same criteria for diagnosis applies when PG is used,<sup>3</sup> although it almost always underestimates the number of obstructive respiratory events, as discussed in a following section. Polygraphy is common in Nordic countries but less so internationally.

### **1.1.3 Prevalence**

In a systematic review from 2017, the prevalence of OSA ranged from 6% to 19% in women and 13% to 33% in men; the overall prevalence in both sexes ranged from 9% to 38%.<sup>4</sup> Geographical differences, different thresholds for diagnosis, and whether symptoms were required or not for diagnosis affected the numbers. The prevalence has sharply risen over the past few decades, as demonstrated by Peppard et al. in an American cohort.<sup>5</sup> The researchers found relative increases of between 14% and 55% depending on age, sex, and the severity of OSA.<sup>5</sup> Increases in the sensitivity in diagnostic criteria, awareness about the condition, and increased levels of obesity are likely explanations.

The prevalence of OSA in Sweden is less studied. However, Franklin et al. showed in a sample from Uppsala that, in 400 women aged 20–70, the prevalence was 50% for OSA of any severity, 20% for moderate OSA, and 6% for severe OSA.<sup>6</sup> The sample was biased towards oversampling, since only responders to a questionnaire on snoring were invited to a follow-up with PSG. The prevalence in Swedish men is unknown.

## **1.2 EVALUATION OF BREATHING DURING SLEEP**

The current section describes procedures and methods used to diagnose and quantify OSA.

### **1.2.1 Recordings**

Objective sleep quality can be measured through different modalities, such as PSG or PG. Polysomnography is the gold standard for evaluating the presence and severity of OSA and can be performed overnight in a sleep laboratory (diagnostic level 1) or ambulant at home (diagnostic level 2). A standard PSG measures breathing and sleep in parallel, as it includes an electroencephalogram, an electrooculogram, an electrocardiogram, an electromyogram, oronasal airflow, oxygen saturation, respiratory movements (thorax and abdomen), sleeping position, carbon dioxide saturation, and video recordings. The examination generates large amounts of data. The most important measure is the number of obstructive apneas and hypopneas per hour of sleep. By recording these, the Apnea-hypopnea index (AHI) can be calculated, thus yielding both the diagnosis and severity of OSA. Another index, closely related to AHI, is the respiratory distress index (RDI), which is AHI with added respiratory effort-related arousals. Table 2 summarizes the 2012 AASM criteria for scoring a PSG.

**Table 2.** Criteria for scoring respiratory events as obstructive apneas, hypopneas, and respiratory event-related arousal, according to AASM 2012

---

Scoring of respiratory events:

Apneas:

- a. Drop in oronasal airflow by  $\geq 90\%$
- b. Event lasts  $\geq 10$  seconds

Hypopneas:

- a. Drop in oronasal airflow by  $\geq 30\%$
- b. Event lasts  $\geq 10$  seconds
- c. Oxygen desaturation of  $\geq 3\%$

Respiratory effort-related arousal:

- a. Increased respiratory effort of  $\geq 10$  seconds leading to arousal from sleep
  - b. Criteria for apnea or hypopnea not met
- 

*Note.* Events should be scored as obstructive with signs of increased inspiratory effort, as specified in the AASM scoring manual.

Although PSG is the gold standard examination, it has its limitations. For example, whether PSG reflects natural sleep or not is debatable, since it is performed in a laboratory more or less comfortably with a large number of attached cords and devices. In addition, several authors have demonstrated that recordings for the same patient may vary on different occasions, a “night-to-night-variability.” On a group level, the results are usually consistent on consecutive nights, but there can still be considerable variability in each individual. For example, Bittencourt et al. demonstrated that, in 20 patients, 50% altered their classification of OSA severity between the first and following nights.<sup>7</sup> Similarly, White et al. showed that, although the mean AHI did not change between different recordings, 35% of patients had a difference in AHI of greater than 10 between nights, indicating significant night-to-night variability.<sup>8</sup> Therefore, some authors suggest that patients should be routinely evaluated for two consecutive nights.<sup>9–11</sup> On the other hand, a review by the SBU (Swedish Agency for Health Technology Assessment and Assessment of Social Services) concluded that one night of PSG would typically be enough.<sup>12</sup> In addition, performing multiple PSG is usually not realistic or economically feasible. A cheaper and simpler alternative would be to perform a PG (level 3), as they are more widely available and allow patients to perform the recording at home. However, since sleep is not recorded, true sleep time, arousals, and sleep stages cannot be assessed. Consequently, real sleep time will likely be overestimated, and hypopneas that cause micro-arousals will be missed. This may result in the underestimation of AHI compared to a PSG, and patients with OSA can be missed. This was shown by Nerfeldt et al. in a study of 187 patients with reported subjective symptoms of OSA (e.g. snoring and Epworth Sleepiness Scale (ESS)  $> 7$ ) but with a “normal” PG (AHI  $< 5$ ). The cohort was examined

with full in-laboratory PSG; 90% were shown to have at least mild OSA, and 10% were diagnosed with severe OSA.<sup>13</sup>

### **1.2.2 Severity classification**

It is widely accepted that the severity of OSA depends on the frequency of obstructive respiratory events, typically AHI. An AHI value of less than 5 is considered normal, an AHI of 5 to 14.9 is considered mild, an AHI of 15 to 29.9 is considered moderate, and an AHI of over 30 is considered severe.<sup>14</sup> This division is useful in everyday clinical practice, but it is not without shortcomings. Although several studies have demonstrated a relationship between severe OSA and comorbidities,<sup>15–18</sup> the cut-offs for the classification between mild and moderate OSA is largely arbitrary and based on a consensus from the AASM Task Force in 1999.<sup>14</sup> The consensus is, in turn, based on an analysis of hypertension within a cohort with OSA<sup>14,19</sup> that showed a substantial increased risk of hypertension at an AHI of approximately 30. The Swedish Transport Agency considers moderate and severe OSA to be a risk in traffic and requires regular medical supervision.

Problematically—and as discussed by Hudgel et al—the criteria for scoring PSG have changed over time, but the criteria for the classification of severity have remained constant.<sup>20</sup> This was highlighted by Ho et al., as the number of apneas substantially varied according to different scoring systems. Within a cohort of 6,641 patients, 8% had severe OSA (according to the 2007 AASM scoring manual criteria A), but this percentage was 18% according to the 2012 AASM manual.<sup>21</sup> The well-known rising prevalence of OSA and the varying prevalence of OSA across different studies should be interpreted in this context. The present studies use the 2007 AASM scoring criteria B ( $\geq 50\%$  flow limitation and  $\geq 3\%$  desaturation or an arousal).

## **1.3 QUESTIONNAIRES**

Subjective sleep quality is usually quantified using different questionnaires, such as the Epworth Sleepiness Scale (ESS)<sup>22</sup> the Karolinska Sleepiness Questionnaire (KSQ),<sup>23</sup> the Functional Outcome of Sleep Questionnaire (FOSQ),<sup>24,25</sup> and the Short Form Health Survey SF-36.<sup>26,27</sup> Ideally, there would be a strong correlation between subjective and objective parameters of sleep; in such circumstances, questionnaires would be possible to use diagnostically. However, although these correlations exist, they have been moderate and not coherent across different studies. For example, Weaver et al. investigated whether results from polysomnography were associated with questionnaires (i.e. ESS, SF-36, and FOSQ) before and after surgery (i.e. radiofrequency tongue and palate reduction or sham surgery); they concluded that the correlation between them was poor.<sup>28</sup> The diagnostic accuracy of the KSQ has also been performed, and only modest correlations found.<sup>29</sup> On

the other hand, both the Sleep Heart Health Study and the Wisconsin Sleep Cohort Study demonstrated associations between SF-36 and OSA.<sup>30,31</sup>

## **1.4 ETIOLOGY AND MORBIDITY**

The previous section described some of the methods used to diagnose OSA and their strengths and weaknesses. The current section examines risk factors for OSA, how normal physiology is disturbed, and the damage that OSA causes.

### **1.4.1 Pathophysiology**

The upper airway is a complicated structure that has evolved to perform different tasks, such as respiration, vocalization, and swallowing, that is, functions that require both flexibility and rigidity. Respiration is also intended to function during sleep, a condition of partial unconsciousness and inhibited sensory and muscle activity. Thus, it is understandable that pathology can occur.

The pathology of OSA is characterized by repeated events of upper airway inspiratory obstruction during sleep. The obstruction site can be at the soft palate and the uvula, the lateral pharyngeal wall, the tonsils, the tongue, or a combination of these.<sup>32,33</sup> This part of the upper airway lacks rigid or bony structures and is therefore partially dependent on active muscular dilation to remain open. The dilatation functions properly in patients who are awake, and patients with OSA do not have any upper airway obstruction while they are awake. During sleep, however, the pharyngeal dilator muscles are less active, and the airway can collapse.<sup>34</sup> This collapse causes an obstruction in the upper airway, with halted or decreased airflow and, eventually, hypoxia.<sup>35</sup> Arousal from sleep is then required to activate dilatation and re-establish an open airway.<sup>36</sup> The cycle thereafter repeats itself any number of times while the patient sleeps.

The severity of the events in every cycle ranges from decreased airflow to full apnea and are associated with asphyxia and fragmented sleep. There are other less abrupt ways than an arousal to keep the upper airway open at inspiration. For example, hypoxia, through the hypoglossal and recurrent laryngeal nerves, stimulates dilatation of the upper airway muscles.<sup>37</sup> The most important stimulus for dilatation of the pharyngeal muscles, however, is negative pressure.<sup>38</sup> Negative pressure naturally occurs at every inspiration due to the Bernoulli principle, which states that an increase in the speed of air simultaneously occurs with a decrease in pressure, hence sucking the tissue inwards. There is evidence to suggest that patients with OSA have an altered reaction to pharyngeal negative pressure. For example, awake patients with OSA have an augmented muscle reaction to negative pressure compared to healthy controls.<sup>39,40</sup> This indicates that the airway of patients

with OSA requires extra stimulus to remain open, even while awake, and perhaps even more so during sleep. There is also data to suggest that dilatation of pharyngeal muscles is not only insufficient but also uncoordinated. Oliven et. al. showed that, in comparison with controls, patients with OSA had a two-fold increased reaction in their genioglossus and simultaneously a decreased reaction in other peripharyngeal muscles. These findings may suggest an out-of-sync response to negative pressure.<sup>41</sup>

Finally, histological and sensory tests imply that patients with OSA can develop nerve<sup>42,43</sup> and muscle<sup>44</sup> lesions over time. This may be attributable to many years of vibrations from snoring, as shown by Friberg et al.,<sup>45</sup> which gradually leads to the development of impaired pharyngeal functions. For example, Jäghagen et al. demonstrated that snoring, with or without OSA, is associated with swallowing dysfunctions compared to non-snoring controls.<sup>46</sup>

#### **1.4.2 Risk factors**

Any condition, trait, or behavior that may cause or increase resistance in the upper airway is a possible risk factor for OSA. Important risk factors include being overweight, smoking, gastroesophageal reflux, alcohol consumption, having a narrow upper airway, age, being male, and a supine sleeping position.

Several studies have demonstrated that being overweight is an independent risk factor for OSA.<sup>5,47,48</sup> For example, Peppard et. al showed that, for every 10% gain in weight, there is a 32% increase in AHI.<sup>49</sup> It has been suggested that obesity causes pharyngeal fat deposition and decreased stability of the trachea. The latter due to abdominal fat pushing the lungs and trachea cranially,<sup>50</sup> also known as “tracheal tug.” Fat deposition in the tongue has also been shown to be correlated to OSA.<sup>51</sup>

In addition, smoking<sup>52</sup> and gastroesophageal reflux<sup>53</sup> have been associated with upper airway inflammation and edema and OSA. Treatment with proton-pump inhibitors seemed to improve OSA by reducing AHI and ESS.<sup>54</sup> Simou et. al showed in a 2018 review that high levels of alcohol consumption were associated with a 25% increase in risk of OSA.<sup>55</sup> One explanation could be alcohol-induced reduction of genioglossal muscle activity.<sup>56</sup>

With regard to anatomical factors, large tonsils are an important risk factor in both men and women.<sup>32,57</sup> However, only approximately 6% of men and women are considered to have large tonsils (i.e. sizes 3 and 4).<sup>57</sup> Mandibular retrognathia appears to be particularly important in women.<sup>57</sup> Aging has been demonstrated to affect both the bony and soft tissue of the upper airway and the pharyngeal reflex to negative pressure,<sup>58</sup> thereby

reducing the ability to compensate for sleep-induced lumen collapse. Accordingly, the prevalence of OSA increases with age.<sup>59–62</sup> Furthermore, OSA is much more common among men than women.<sup>5,61</sup> It has been suggested that these dissimilarities are explained, among other factors, through differences in fat distribution, as men add weight predominantly in the neck, tongue and viscera compared to women.<sup>63</sup> Men who gain weight are also more likely to experience worsened nocturnal breathing compared to women who gain weight.<sup>47</sup>

Lastly, sleeping in a supine position has been shown to aggravate OSA. In a study of 574 patients with OSA, the respiratory distress index (RDI) more than doubled in a supine sleeping position compared to a lateral sleeping position in 56% of the patients.<sup>64</sup>

### **1.4.3 Morbidity and mortality**

Obstructive sleep apnea is associated with several important negative health consequences. For example, OSA increases the risk of cardiovascular diseases<sup>15,65</sup> such as hypertension,<sup>66,67</sup> congestive heart failure,<sup>68</sup> fatal and non-fatal myocardial infarction,<sup>15</sup> and stroke.<sup>69,70</sup> There is also evidence for a more than threefold increase in traffic accidents.<sup>71</sup> In addition, studies have reported increased risk of cancer,<sup>18,72,73</sup> metabolic disorders,<sup>74,75</sup> and all-cause mortality.<sup>17</sup>

The physiological pathways between OSA and its negative consequences are complex and not fully understood. Intermittent episodes of hypoxia and arousals have been linked with increased levels of reactive oxygen species, angiogenesis, elevated sympathetic activation, platelet activation and aggregability, and systemic and vascular inflammation.<sup>65,76</sup> All of these factors are believed to contribute to the diversity in morbidity for patients with OSA.



## 1.5 TREATMENT

Any OSA treatment aims to open up or prevent the collapse of the upper airway in order to ease breathing during sleep. There are several treatments, indicating that none is better than others in all aspects.

### 1.5.1 Non-surgical treatments

#### 1.5.1.1 *Continuous positive airway pressure*

In 1981, Sullivan et al. introduced continuous positive airway pressure (CPAP),<sup>77</sup> which is now the gold standard therapy for OSA. This treatment opens the upper airway by delivering positive pressure through an oronasal or nasal mask. When used as prescribed, CPAP is highly effective; a Cochrane report from 2006 concluded that CPAP reduces symptoms of sleepiness and improves quality of life and nocturnal respiratory parameters.<sup>78</sup> In addition, CPAP has been shown to reduce all-cause mortality<sup>17</sup> and the risk of cardiovascular events.<sup>15</sup> Nasal mask have been suggested to be more effective than oronasal masks in treating OSA, perhaps since the oral portion of the oronasal mask pushes the tongue backwards, thus blocking the pharynx.<sup>79,80</sup>

The main disadvantage of CPAP lies in its adherence. Some studies have reported an adherence rate of only 29–68%,<sup>81–84</sup> and adherence does not seem to have improved over a 20-year period despite behavioral interventions and improvements in machine technology.<sup>85</sup> On the other hand, a study from 2019 that used a large database of more than 2.5 million CPAP users revealed an adherence rate of 75% and a mean of 5.1 hours of use per night.<sup>86</sup> However, although this likely is the largest study on the topic, it was limited in that it only analyzed data from patients who initiated treatment and collected their devices, thus excluding patients who refused to start treatment at all.

#### 1.5.1.2 *Mandibular retaining device*

A mandibular retaining device (MRD) is a dental device that opens the upper airway by moving the mandible forward. This prevents the tongue from falling back and blocking the pharynx, much like the jaw thrust performed for unconscious patients. Though not as effective as CPAP, a Cochrane report found that an MRD improved both symptoms of sleepiness and nocturnal respiratory parameters.<sup>87</sup> However, when tested against a placebo device, Marklund et al. found no improvements in subjective parameters.<sup>88</sup> The rate of adherence with an MRD is in line with CPAP—approximately 56–68%. Common reported side effects include excessive salivation, dry mouth, and tooth and jaw discomfort<sup>89</sup>.

#### *1.5.1.3 Weight reduction*

Losing weight is an effective treatment for OSA, and a randomized controlled trial (RCT) found a 67% reduction in AHI compared to controls with a low-energy diet intervention.<sup>90</sup> The results were stable at the one-year follow-up.<sup>91</sup> A meta-analysis in 2013 came to a similar conclusion.<sup>92</sup> Peppard et. al demonstrated that a 10% reduction in weight predicted a 26% decrease in AHI.<sup>49</sup>

#### *1.5.1.4 Proton-pump inhibitors*

There is some evidence to suggest that proton-pump inhibitors improve OSA in selected patients,<sup>54</sup> possibly by reducing posterior commissure edema,<sup>53</sup> thus enlarging the upper airway.

#### *1.5.1.5 Positional training*

Since OSA commonly worsens in a supine position,<sup>64</sup> a possible treatment would be to reduce sleeping time in this position. There are several ways to achieve this, such as with special pillows, the “snore belt,” the “tennis ball,” or vibrating alarms. A Cochrane report from 2020 analyzed eight studies and concluded that positional training is less effective than CPAP but more effective than no treatment at all.<sup>93</sup>

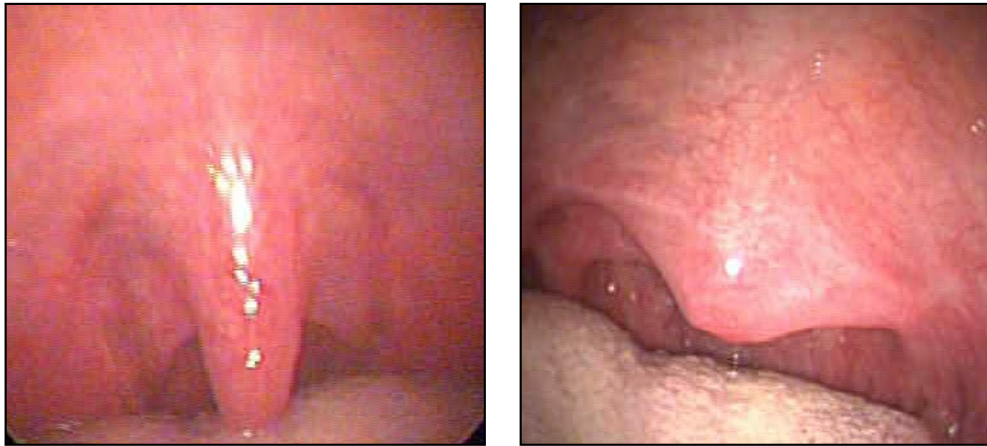
### **1.5.2 Surgical treatments**

#### *1.5.2.1 Uvulopalatopharyngoplasty*

Since it was first described by Fujita in 1981, uvulopalatopharyngoplasty (UPPP) has been the dominant surgical method for treating OSA.<sup>94</sup> As the first alternative to tracheostomy, UPPP represented a major step forward. It combines conventional tonsillectomy (TE) with a reduction of the soft palate and uvula. A modified and conservative method is used at our clinic (see Figures 2 and 9). Two RCTs demonstrated positive effects of UPPP. Browaldh et al. demonstrated a 60% reduction in AHI (AHI 53.3 to 21.1 events/h), without any serious complications.<sup>95</sup> Sommer et. al reported similar findings, with 20 out of 31 patients being successfully treated (defined as AHI < 15 after surgery). In addition, 38 out of 39 patients reported being satisfied with the outcome of their surgery,<sup>96</sup> with a decrease in AHI of 33.7 to 15.4 events per hour.

A multi-center RCT by Mackay et. al in 2020 demonstrated a reduction in AHI from 47.9 to 20.8 events per hour<sup>97</sup> after UPPP (combined with radiofrequency tongue reduction). The cohort was rather similar to the one in SKUP3, with the important exception of the inclusion of Friedman stage III patients (see patient selection in Section 1.5.3). However, the surgical method was more radical, with incisions of the palatopharyngeus muscle in addition to the tongue reduction.

In 2016, a statement from the Swedish Health Technology Assessment concluded that “UPPP may be an option in selected patients where no other treatment remains.”<sup>98</sup> Similarly, Rosvall et. al concluded in 2017 that there is level 1 evidence for UPPP in selected patients.<sup>99</sup>



**Figure 2.** Pictures of modified uvulopalatopharyngoplasty (UPPP). The picture on the left is from before UPPP, and the one on the right is six months after surgery. Photos by Danielle Friberg.

#### *1.5.2.2 Side effects*

Given their high effectiveness and non-invasive nature, patients should be offered CPAP and MRD as a first-line treatment. However, for patients who find it difficult to adhere to these treatments, UPPP might be a suitable alternative as “salvage surgery.” Until recent years, the evidence for UPPP was poor and even argued against surgery due to adverse events. For example, both a Cochrane report<sup>100</sup> and a Nordic meta-analysis<sup>12</sup> concluded that there was not enough evidence to recommend surgery. In addition, a meta-analysis from 2009 concluded that adverse events were both common and serious.<sup>101</sup> For example, persistent side effects occurred in more than half of the patients, including difficulty swallowing (31%), voice changes (13%) and taste disturbances (5%). Värendh et. al. demonstrated similar findings in a cohort of 129 patients who underwent surgery between 1985 and 1991. A questionnaire reported remaining side effects in 38% of the patients; in a subgroup of patients who used CPAP, 71% reported that they would not have undergone surgery had they known about the consequences in advance.<sup>102</sup> However, the studies included multiple surgical techniques, some more radical than others and some of which involved laser. The selection of patients was also different at the time, since there was no established alternative treatment except for tracheotomy, and the CPAP was only at the beginning of becoming widely available.

#### *1.5.2.3 Hypoglossal nerve stimulation*

Hypoglossal nerve stimulation opens the upper airway through electrical stimulation of the genioglossus muscle through the hypoglossal nerve. A sensor is connected to inspiratory thoracic muscles, and a stimulating electrode is connected to the hypoglossal nerve. Regarding efficacy, there are an increasing number of interventional studies with positive results. For example, in a cohort of 129 highly selected patients (e.g. BMI < 32, AHI > 20 but < 50, tonsil size < 3 and favorable DISE without concentric collapse retropalataly), Strollo et al. demonstrated a decrease in AHI from 29.3 to 9 events per hour<sup>103</sup> and stable long-term results (five years).<sup>104</sup> From the same cohort, a subgroup of 46 patients with successful implantation were further evaluated in an RCT that compared continued stimulation versus withdrawal (i.e. stimulation turned off for one week). The study showed that AHI reverted to baseline in the withdrawal group, but the improvement returned when stimulation was turned on again.<sup>105</sup> In addition, a meta-analysis from 2019 that included 19 studies demonstrated that results were generally favorable to hypoglossal nerve stimulation, with a mean improvement in AHI of 25 events per hour.<sup>106</sup> A combination of UPPP and hypoglossal nerve stimulation might also be beneficial.<sup>107</sup> Hypoglossal nerve stimulation has not been introduced in Sweden.

#### *1.5.2.4 Maxillomandibular advancement*

Maxillomandibular advancement opens the airway through surgically achieved protrusion of the mandibula and maxilla by approximately 10 mm. It is arguably one of the more effective surgical procedures for OSA, with a mean reduction of AHI by approximately 80%, according to a 2016 meta-analysis with pooled data from 455 patients.<sup>108</sup> Among 267 patients with available data, 74% had undergone previous upper airway surgery; this indicates that maxillomandibular advancement, due to its very invasive character, is rarely the first line of treatment. Risks includes malocclusion, pain, and unwanted cosmetic results.

#### *1.5.2.5 Bariatric surgery*

In obese patients with OSA, bariatric surgery may be an option. A meta-analysis from 2009 showed a significant mean reduction in AHI of 38.2 from a baseline of 54.7 events per hour.<sup>109</sup> However, an RCT in 2012, which compared a conventional weight loss program with gastric banding in 60 patients, did not result in a significant reduction in AHI despite significant weight loss. The AHI improved, with 14 events per hour in the weight loss group and 25.5 events per hour in the surgery group.<sup>110</sup>

#### *1.5.2.6 Tracheostomy*

Tracheostomy is a very effective treatment for OSA and has been shown to often normalize nocturnal breathing.<sup>111</sup> However, it is rarely used today since there are less invasive alternatives.

#### *1.5.2.7 Tonsillectomy*

Tonsillectomy improves nocturnal respiration and daytime sleepiness in selected patients, as demonstrated in a systematic review<sup>112</sup> and in a Swedish prospective intervention study.<sup>113</sup> This treatment is discussed in relation to UPPP in the section on future perspectives (Section 7).

### **1.5.3 Patient selection for uvulopalatopharyngoplasty**

In a 1996 meta-analysis, Sher et al. highlighted that the success rate after UPPP in unselected patients was only 41% (success was defined as a 50% reduction in RDI and < 20).<sup>114</sup> Possible explanations could be that the selection of patients was inadequate and that the surgery did not address the actual obstruction site. The exact obstruction site, however, has proven to be difficult to determine. A proposed method is the Müller maneuver (MM). The MM is performed in an awake patient using a transnasal flexible endoscope to view the hypopharynx, velopharynx and oropharynx while forcefully inhaling against a closed nose and mouth (reversed Valsalva). It has merit in its simplicity but demonstrates weak or conflicting correlations to surgical outcomes. For example, in a study of 30 patients undergoing UPPP, the MM did not have any significant predictive value.<sup>115</sup> In a slightly better set of results, Kantsantonis et al. showed that the MM could predict success (defined as a 50% reduction in AHI) in 12 out of 24 patient.<sup>116</sup> In addition, Aboussouan et al. showed a success rate of 78% in patients with velopharyngeal collapse only, compared with 36% patients with additional collapse of the tongue.<sup>117</sup>

Ideally, patients would be asleep when being examined for the site of obstruction. A theoretically promising method is drug-induced sleep endoscopy (DISE),<sup>118</sup> a procedure that attempts to mimic sleep. It is used internationally in some sleep centers and in research but has not been introduced in Sweden. Several studies have shown that DISE changes surgical planning,<sup>119</sup> but correlation with actual surgical outcomes appears to be weak.<sup>120,121</sup> There are, however, some indications of a correlation between findings of obstruction in the lateral walls and tongue<sup>122</sup> and surgical outcomes. There is also some evidence of advantages in the selection of patients for upper airway nerve stimulation.<sup>123</sup>

In 2002, Friedman et al. developed a clinical staging system to select patients with OSA who were likely to benefit from intervention through UPPP. The system combined tonsil size and tongue position to predict the likelihood of successful surgery, as are shown in Table 3.

**Table 3.** The Friedman staging system

Friedman stage	Friedman tongue position	Tonsil size	Success rate
I	1, 2	3, 4	81%
II	1, 2	1, 2	38%
	3, 4	3, 4	
III	3, 4	1, 2	8%

*Note.* The Friedman stage is determined by combining the Friedman tongue position with tonsil size. A lower stage is associated with better surgical outcomes. Patients with a BMI over 40 were considered to fall into Friedman stage III regardless of tongue position or tonsil size.

Friedman sorted 134 patients with OSA into three different stages and correlated the stages with surgical success (i.e. a post-operative RDI of less than 20 and reduced by at least 50%). Patients had an 81% success rate if Friedman stage I, 38% if Friedman stage II, and 8% if Friedman stage III.<sup>124</sup> In 2006, Hsueh-Yu Li et al. confirmed a similar order of correlation in 110 patients.<sup>125</sup> As with any clinical test, the results can be expected to vary among different examiners and therefore affect the inter-examiner agreement. The designers of the system (Friedman et al.) found a high inter-examiner agreement, with a kappa value of 0.83 (indicating very good agreement), by using video clips of oropharyngeal examinations.<sup>126</sup> Patients with a BMI over 40 were classified as stage III regardless of tonsil size or tongue position. No study of inter-examiner agreement with patients in a clinical setting have previously been performed.

## 2 AIMS

The overall aim of this thesis was to evaluate uvulopalatopharyngoplasty in terms of patient selection for surgery, sleep quality after surgery, side effects after surgery, and long-term subjective and objective results.

More specifically, the aims were as follows:

- To evaluate the Friedman staging system by determining the inter-examiner agreement of one of its key components, the Friedman tongue position (**Study I**) and by determining the inter-examiner agreement of the Friedman stage in a clinical setting on patients with obstructive sleep apnea (**Study II**)
- To evaluate whether uvulopalatopharyngoplasty improves subjective sleep quality in patients with obstructive sleep apnea by using the Karolinska Sleep Questionnaire and the Functional Outcomes of Sleep Questionnaire (**Study III**)
- To evaluate long-term satisfaction and side effects after uvulopalatopharyngoplasty through questionnaires and telephone interviews (**Study IV**)
- To investigate whether uvulopalatopharyngoplasty remained effective eight years after surgery by using polysomnography and the Epworth Sleepiness Scale and to evaluate whether any baseline factors could predict the long-term outcomes (**Study V**)

## 3 METHODS

### 3.1 OVERVIEW OF STUDIES

The studies in this thesis used a descriptive observational, prospective interventional, or randomized controlled design, as summarized in Table 4.

**Table 4.** Overview of studies included in this thesis

Study	Design	Population	Inter- vention	Comparison	Outcomes	Follow-up
I-II	Descriptive observational	Medical doctors, patients with OSA	-	-	Inter-examiner agreement from Cohen's kappa	-
III	Randomized controlled study	18–65 years, moderate to severe OSA	UPPP	Intervention vs. controls	Sleep quality from questionnaires (FOSQ and KSQ)	Six months, two years
IV	Prospective interventional	18–65 years, moderate to severe OSA	UPPP	Before and after surgery	Side effects and satisfaction from questionnaire and interviews	Six months, two years, nine years
IV	Prospective interventional	18–65 years, moderate to severe OSA	UPPP	Before and after surgery	Sleep quality from polysomnography and questionnaire (ESS)	Eight years

*Note.* “OSA” refers to obstructive sleep apnea, “FOSQ” refers to the Functional Outcome of Sleep Questionnaire, “UPPP” refers to uvulopalatopharyngoplasty, and “KSQ” refers to the Karolinska Sleep Questionnaire.

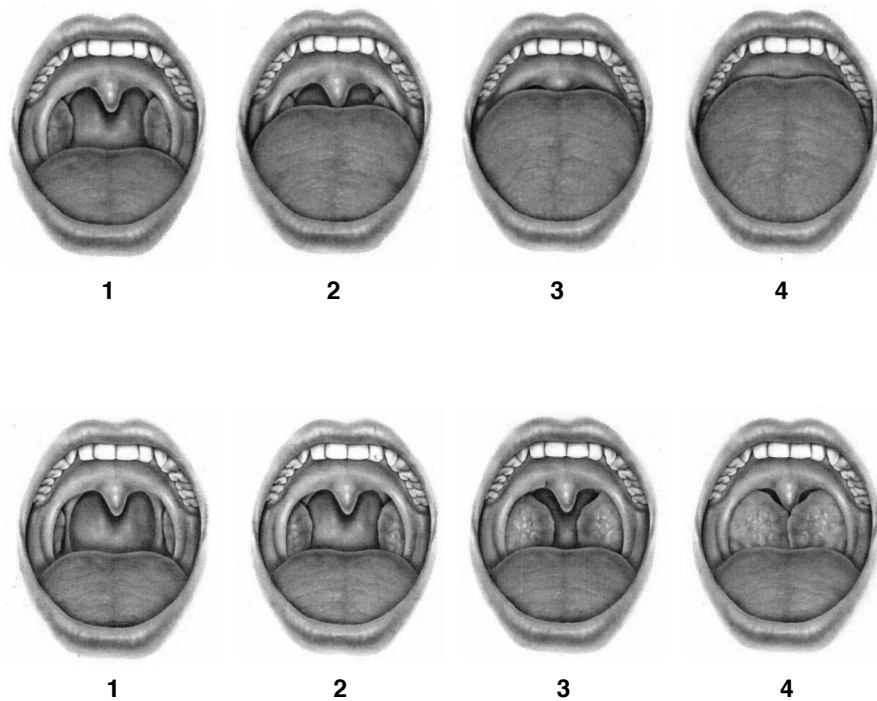
### 3.2 STUDY I AND STUDY II – THE FRIEDMAN STAGING SYSTEM

#### 3.2.1 Study design

Study I and study II had a similar design; the former could be considered a pilot study for the latter. In study I, the inter-examiner agreement for the Friedman tongue position was evaluated and, in study II, both the Friedman tongue position and tonsil size were evaluated, enabling the determination of the clinically relevant Friedman stage. In study I, medical colleagues participated and examined each other. In study II, patients with OSA



were examined by doctors in a clinical setting. Friedman tongue position and tonsil size are shown in Figure 3, and the Friedman staging system is shown in Table 3.



**Figure 3.** Friedman tongue position and tonsil size. The first row illustrates the four possible Friedman tongue positions, while the second row illustrates the four different tonsil sizes. Courtesy of Friedman and co-authors.

Eleven residents and four ear, nose, and throat (ENT) specialists participated in study I. The study was performed in a lecture hall with conventional headlights. The participants knew about the Friedman tongue position, but the extent to which they had used it in clinical practice varied. All were given verbal and written instructions and pictures to compare with. Instructions were given in the same manner as in Friedman et al.'s original study.<sup>124</sup> That is, the test subjects were asked to open their mouths wide without sticking out their tongue, to repeat this procedure five times, and to note the most consistent value. Every participant then examined each other, resulting in a total of 210 evaluations.

In study II, 12 patients with OSA who were under evaluation for UPPP were examined by 14 doctors, of whom two were specialists in sleep medicine, nine were ENT specialists, and three were ENT residents. All had used the Friedman staging system before but to varying degrees. A conventional ENT exam room and equipment were used. To evaluate tonsil size, the use of a tongue depressor was allowed if necessary. Every doctor then examined every patient, resulting in a total of 168 evaluations. Each doctor noted their

findings on pre-printed templates and kept them hidden from the patient and other doctors to avoid bias.

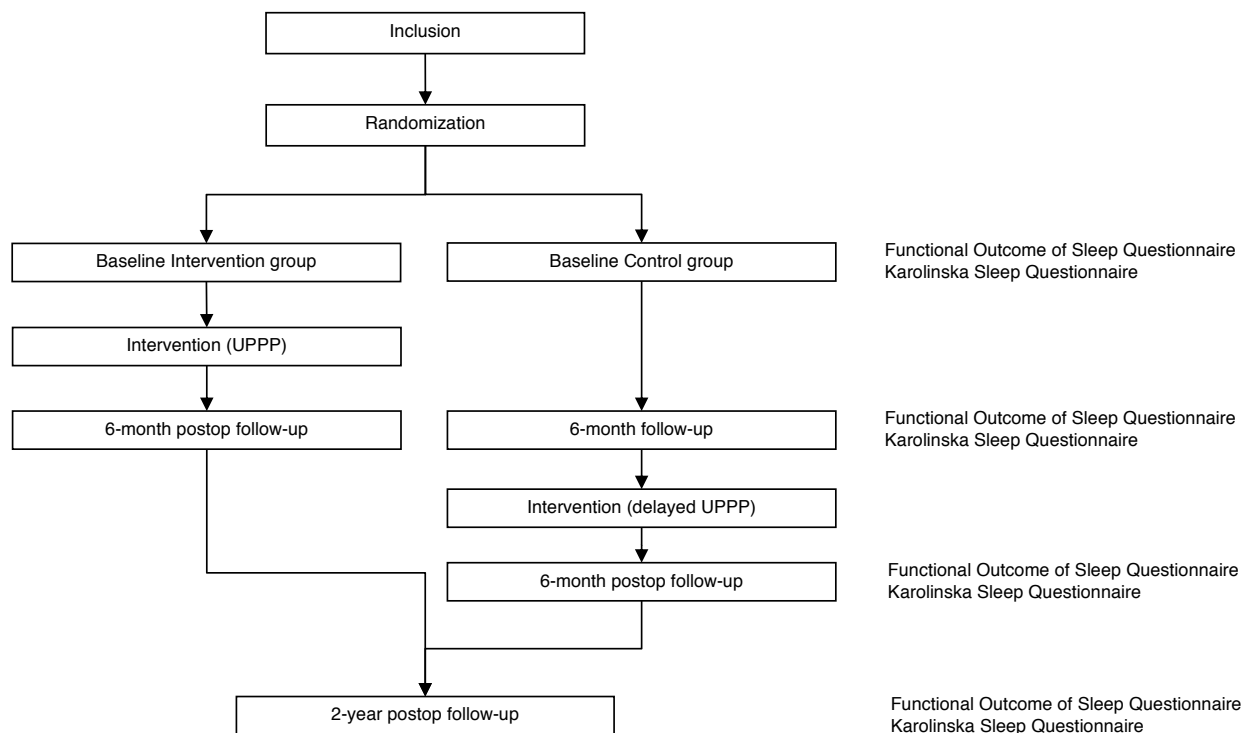
### 3.2.2 Outcomes

Inter-examiner agreement was analyzed using Cohen's kappa and presented as a median with first and third quartiles.

## 3.3 STUDY III – SLEEP QUALITY AFTER UVULO PALATO-PHARYNGOPLASTY

### 3.3.1 Study design

The study consisted of a two-part analysis of secondary data: the first part was a randomized controlled trial performed by Browaldh et al. in 2013 (SKUP3)<sup>95</sup> with two study groups (intervention and controls), and the second part was a post-operative follow-up of all patients (intervention and controls who received delayed surgery) at six and 24 months after surgery. The flow of patients is illustrated in Figure 4.



**Figure 4.** Flowchart of patients in study III. The figure shows the two study arms in the randomized controlled trial and where they merge (six months post-operative follow-up) to a post-operative follow-up of all patients. “UPPP” refers to uvulopalatopharyngoplasty.

All patients with OSA referred to the ENT department of the Karolinska University Hospital were eligible for inclusion. All patients underwent clinical investigations by ENT specialists with fiber endoscopy of the upper airways. Patients who were considered suitable and willing to undergo surgery were asked to participate in the study. The most important inclusion criteria were moderate or severe OSA, an ESS value greater or equal to 8, a body mass index of less than 36 kg/m<sup>2</sup>, Friedman stage I or II, and non-adherence to CPAP and MRD treatments. Inclusion and exclusion criteria are stated in full in paper III.

### **3.3.2 Part 1 – Randomized controlled trial**

First, the patients were examined at baseline using PSG, questionnaires, and a vigilance test (the modified Oxford Sleep Resistance test or OSLER, performed once). Then, they were randomized to either the intervention (UPPP) or control group (delayed surgery). Follow-up for both groups took place six months after surgery using PSG, questionnaires, and vigilance test. The results from the questionnaires were then compared and correlated to results from PSG and the vigilance test.

### **3.3.3 Part 2 – Post-operative follow-up of all patients**

Since the control group in the RCT received delayed surgery, all patients (intervention and controls) could be evaluated as a single cohort in a post-operative follow-up. The follow-ups were performed at six and 24 months after surgery using PSG and questionnaires.

### **3.3.4 Outcomes**

Developed by Weaver et al. in 1997, the Functional Outcomes of Sleep Questionnaire (FOSQ) is a 30-item questionnaire that includes a total score and five subscales.<sup>25</sup> The FOSQ measures sleep-specific quality of life, that is functions of everyday life in relation to sleepiness thus, in contrast to the Karolinska Sleep Questionnaire (KSQ), the FOSQ does not only measure patients' perceptions of their sleep quality. The subscales consist of general productivity, social outcome, activity level, vigilance, and intimate relationships. Responses range from 1 to 4, where 1 indicates extreme difficulty and 4 indicates no difficulty. A score of 0 is also possible for some questions with the alternative response, "I don't do this activity for other reasons." A normal total score is considered to be higher than 18<sup>127</sup> and the maximum is 20. An increase of one point has been suggested to be clinically relevant.<sup>127</sup> This study used a validated Swedish version of the FOSQ.<sup>24</sup> Examples of questions are provided in Table 5, with one question from each subscale.

**Table 5.** Examples of questions from each subscale in the Functional Outcome of Sleep Questionnaire

- 
- Do you have difficulty operating a motor vehicle for long distances (greater than 100 miles) because you become sleepy or tired? (Vigilance, Question 7)
  - Do you have difficulty maintaining a telephone conversation, because you become sleepy or tired? (General productivity, Question 11)
  - Do you have difficulty visiting with your family or friends in their home because you become sleepy or tired? (Social outcome, Question 13)
  - Do you have difficulty keeping pace with others your own age because you are sleepy or tired? (Activity level, Question 25)
  - Has your desire for intimacy or sex been affected because you are sleepy or tired? (Intimate relationships, Question 28)
- 

*Note.* The name of the subscale followed by the question number are given in parentheses.

The KSQ measures subjective sleep, sleepiness, and patients' perceptions of their sleep and sleepiness. The 1992 version of the KSQ included several sections. The first part consisted of 17 questions; seven referred to sleep quality (insomnia symptoms), three to snoring and cessation of breathing (symptoms of sleep apnea), and five to sleepiness and fatigue during the daytime (symptoms of sleepiness).<sup>128</sup> Responses to the two remaining questions in the KSQ about nightmares (Question g) and sleeping too few hours (Question k) were excluded from the present study, since nightmares are uncommon among adults and sleeping too few hours is considered a control question, according to Nordin et al.<sup>23</sup> Thus, the current study evaluated responses from 15 questions. Responses ranged from 0 to 5, where 0 means never and 5 means always. The three subscales of the KSQ are named insomnia, apnea, and sleepiness.

Low scores in the KSQ means better sleep. There is no standard interpretation of what is considered normal or clinically relevant. The KSQ is shown in Figure 5. (The KSQ is not to be confused with the Karolinska Sleepiness *Scale*, which is a nine-point Likert scale measuring sleepiness at a particular time of day.)

**Have you experienced any of the following complaints the past three months?**

	Never	Rarely	Some- times	Often	Mostly	Always
		<i>A few times</i>	<i>Several times per mo.</i>	<i>1-2 times per week</i>	<i>3-4 times per week</i>	<i>5 times or more per week</i>
a) Difficulties falling asleep	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b) Difficulties waking up	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c) Repeated awakenings with difficulties going back to sleep	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d) Heavy snoring	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
e) Gasping for breath during sleep	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
f) Cessation of breathing during sleep	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
g) Nightmares	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
h) Not feeling refreshed when waking up	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
i) Premature awakening	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
j) Disturbed/restless sleep	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
k) Insufficient amount of sleep	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
l) Feeling exhausted when waking up	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
m) Sleepiness during work	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
n) Sleepiness during leisure time	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
o) Unintentional dozing off during work	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
p) Unintentional dozing off during leisure time	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
q) Having to fight off sleep to stay awake	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

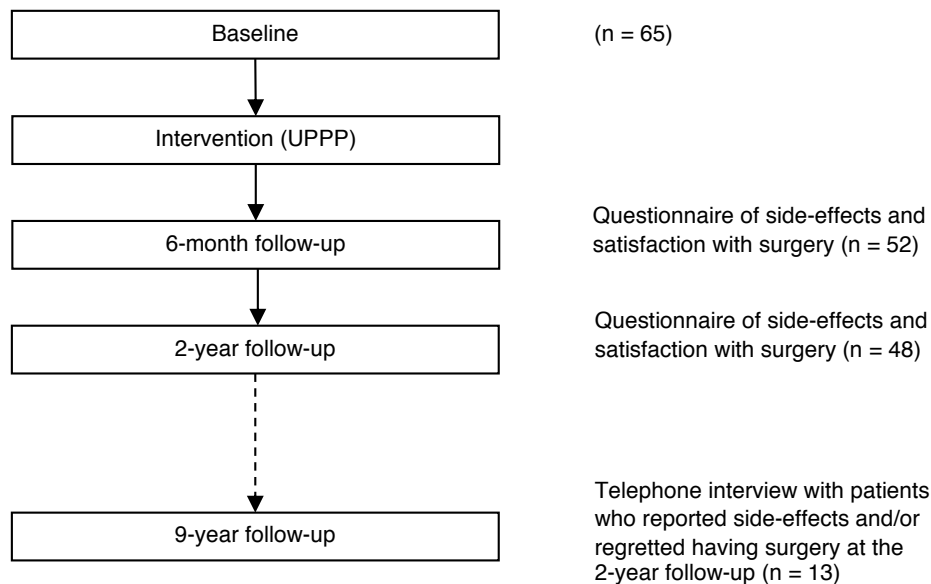
**Figure 5.** The 1992 version of the Karolinska Sleepiness Questionnaire (KSQ). Reprinted with permission from *Stressforskningsinstitutet*.

### 3.4 STUDY IV – SIDE EFFECTS AFTER UVULOPALATO-PHARYNGOPLASTY

#### 3.4.1 Study design

Similar to the second part of study III, all patients who underwent surgery were evaluated as a single cohort using a questionnaire at six and 24 months after surgery. The questionnaire evaluated side effects, satisfaction with surgery, and whether or not patients would

recommend surgery to others. Patients who reported side effects or regretted having surgery at the 24-month follow-up were contacted for an individual interview. Figure 6 provides an outline of the study.



**Figure 6.** Outline of study IV with follow-ups and procedures at follow-up. “UPPP” refers to uvulopalatopharyngoplasty and “n” refers to the number of participants.

### 3.4.2 Outcomes

#### 3.4.2.1 *Questionnaire of side effects and satisfaction with surgery*

There were five questions in the questionnaire, and patients could answer yes or no:

1. Are you satisfied with the surgery?
2. Do you regret the surgery?
3. Would you recommend it to others?
4. Do you have any taste disturbances?
5. Do you have any inconveniences and/or side effects after surgery (combined as “side effects”)?

Patients were also instructed to rate their side effects using a four-point Likert scale (none = 0, mild = 1, moderate = 2, and severe = 3) and describe them in free text. The questionnaire was constructed by our research group and not externally validated.

#### 3.4.2.2 *Interview*

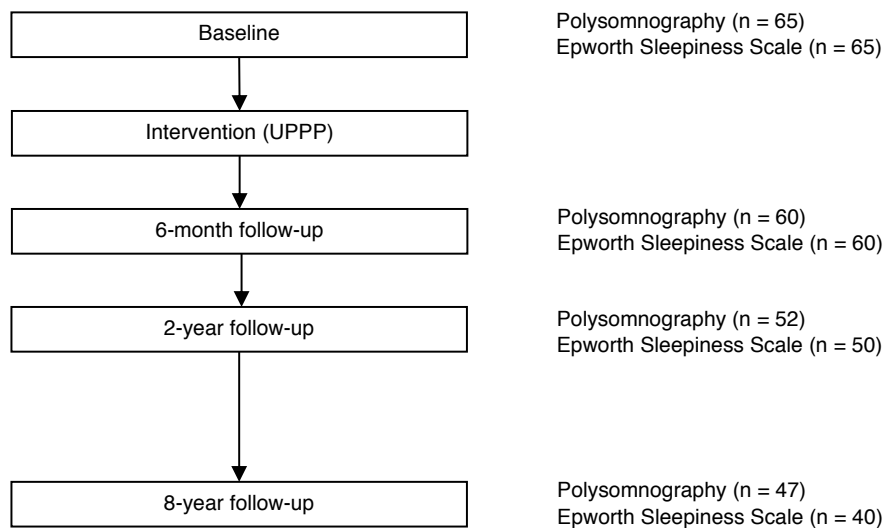
All participants who regretted having surgery or reported side effects at the 24-month follow-up were contacted for a five- to ten-minute telephone interview. The call took

place at a mean timeline of nine years after surgery. The aim of the telephone interview were to (1) provide patients with an opportunity to give a detailed account of their side effects and reasons for regretting surgery, (2) determine if side effects persisted (and if so, how often they occurred and to what degree), and (3) ask if patients were dissatisfied with the surgery after nine years and why.

### 3.5 STUDY V – EIGHT-YEAR FOLLOW-UP AFTER UVULOPALATO-PHARYNGOPLASTY

#### 3.5.1 Study design

The entire cohort of all patients who underwent surgery from the RCT SKUP3 were offered follow-up with PSG and questionnaires approximately eight years after surgery. The outline of the study is shown in Figure 7.



**Figure 7.** Outline of study IV with follow-ups and procedure at follow-up. “UPPP” refers to uvulopalatopharyngoplasty and “n” refers to the number of participants.

At this stage, the only criteria for exclusion were unwillingness to participate or moving out of Stockholm district. The outcomes were respiratory data from PSG, ESS score, and a regression analysis to identify baseline factors that could predict long-term PSG results.

#### 3.5.2 Outcomes

##### 3.5.2.1 Polysomnography

An in-laboratory PSG was used at each follow-up. To enable comparison over time without results being affected by changes in scoring criteria, the 2007 AASM criteria B (i.e.

flow reduction of at least 50% leading to a 3% oxygen desaturation or arousal) were used at all follow-ups despite the 2012 AASM criteria (see Figure 3) being available by the time of the final follow-up. The results were interpreted based on standard ranges (normal = AHI < 5, mild = AHI 5–14.9, moderate = AHI 15–29.9, and severe = AHI ≥ 30 events/h). Surgical success was defined as AHI less than 20 and a 50% reduction in AHI.

### 3.5.2.2 The Epworth Sleepiness Scale

The Epworth Sleepiness Scale is a self-reported questionnaire with eight questions rated on a four-point Likert scale (0–3). The ESS score evaluates the risk of dozing off or falling asleep during eight common activities. Scores range from 0 to 24; the higher the score, the higher the average daytime sleepiness. The Swedish validated version<sup>129</sup> was used. The minimum clinically important improvement has been suggested to be between 2 and 3.<sup>130</sup> The results were interpreted according to reference criteria, in which normal is equal to 0–10; mild is equal to 11–12, moderate is equal to 13–15, and severe is equal to 16–24. The Epworth Sleepiness Scale is shown in Figure 8.

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired?  
 This refers to your usual way of life recently.  
 Even if you haven't done some of these things recently, try to figure out how they would have affected you.  
 Use the following scale to choose the **most appropriate number** for each situation:

- 0 = **no chance** of dozing
- 1 = **slight chance** of dozing
- 2 = **moderate chance** of dozing
- 3 = **high chance** of dozing

*It is important that you answer each item as best as you can.*

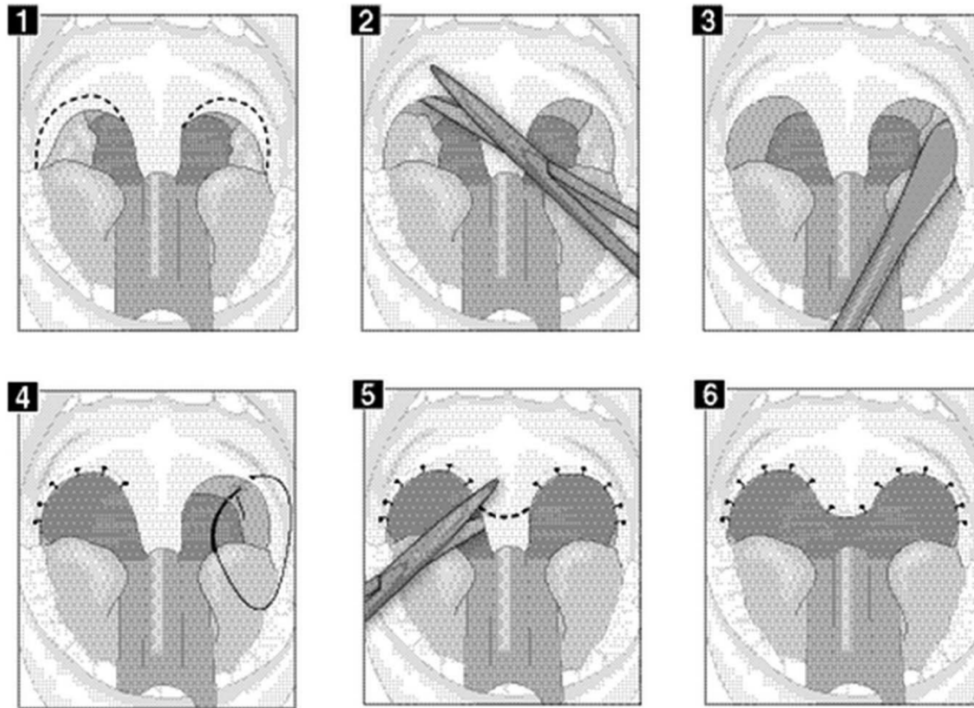
Situation	Chance of Dozing (0-3)
Sitting and reading _____	_____
Watching TV _____	_____
Sitting inactive in a public place (e.g., a theater or a meeting) _____	_____
As a passenger in a car for an hour without a break _____	_____
Lying down to rest in the afternoon when circumstances permit _____	_____
Sitting and talking to someone _____	_____
Sitting quietly after a lunch without alcohol _____	_____
In a car or bus, while stopped for a few minutes in traffic _____	_____

**Figure 8.** The Epworth Sleepiness Scale. ESS © MW Johns 1990-1997. Used under license.



### 3.6 MODIFIED UVULOPALATOPHARYNGOPLASTY

All study participants underwent surgery at the ENT department of Karolinska University Hospital. The procedure was a modified version of the UPPP described in 1981 by Fujita et al.<sup>94</sup> It was performed under general anesthesia with a nasal tube. The procedure is described in Figure 9. Hemostasis was primarily achieved with compression and, if needed, with careful local bipolar diathermia.



**Figure 9.** Modified uvulopalatopharyngoplasty. (1) Marked excision line laterally to the uvula. (2) Excision of the anterior tonsillar pillar 2–3 mm and the mucosa between the pillars. (3) Tonsillectomy with cold steel (Henke). (4) Single sutures (the 'loop' consists of needle and thread) lift the posterior pillar, along with the palatopharyngeal muscle, to the anterior pillar, also with suturing of the soft palatal mucosa. (5) Amputation of the uvula, leaving approximately 1 cm. (6) Final result.

Our surgical safety program at the time of the study included peri- and post-operative tranexamic acid (five days) and penicillin prophylaxis (three days). Diclofenac and tramadol were used as painkillers. Patients with moderate OSA were kept six to 12 hours in the post-operative recovery room, and patients with severe OSA were kept for 12 to 24 hours.

### 3.7 STATISTICAL CONSIDERATIONS

Throughout the studies, parametric data such as PSG, BMI, age, and the vigilance test were described using mean and standard deviation and analyzed with paired or unpaired parametric t-tests, when normally distributed. Ordinal data such as scores from questionnaires and clinical tests (e.g. tonsil size, Friedman stage, and Friedman tongue position) were described using median and interquartile ranges and analyzed with unpaired (Mann–Whitney U) or paired (Wilcoxon signed-rank) non-parametric tests. To facilitate comparisons with previous studies, some ordinal data from questionnaires were presented as mean in addition to median. For correlation analyses between PSG and the questionnaires, a non-parametric Spearman’s rank correlation test was used.

Cohen’s kappa (**studies I and II**) measures the degree of agreement between different examiners that occurs beyond what would be explained by chance. Kappa values usually range between 0 and 1, where 0 represents agreement that would be expected from random chance and 1 represents perfect agreement. Negative values (down to -1) are unlikely but possible and represent an agreement that is even less than that would be expected from random chance. There is no generalized interpretation of what a “good” or “bad” kappa would be; it largely depends on what is clinically acceptable. To enable comparison with previous studies, we used interpretations suggested by Byrt<sup>131</sup> and Altman.<sup>132</sup>

A non-response analysis was performed in **studies III and V** to evaluate dropouts. The baseline AHI and questionnaires (KSQ, FOSQ, and ESS) for the group without values at the follow-ups were compared with the group with values at the follow-ups. In addition, sensitivity analyses were performed for AHI and ESS values for all of the 65 included patients in **study V**. An intention-to-treat analysis was conducted for all patients randomized in **study III**. Variables in the sensitivity analysis and intention-to-treat analysis were imputed to “no change from baseline” when follow-up was missing, “no change from follow-up” when baseline was missing, or “median of baseline” when both baseline and follow-up was missing.

As follow-up time increases, more dropouts can be expected. This can be addressed by only analyzing patients who completed the follow-up and excluding the others. However, this also means more lost data on baseline. Both methods were used and presented in **study V**.

Multiple linear regression analysis was used in **study V** to evaluate baseline factors of clinical value that could predict long-term results. The regression model was constructed with stepwise backward elimination. Only statistically significant predictors were included in the final model.

#### 3.7.1.1 *Software*

The software R, R Core Team, 2017 (studies I to II), Statistica 10.0 (studies III to V), and Stata 13.1 (study I to III and V) were used for statistical analyses. A p-value of less than .05 was considered to be significant.

### 3.8 ETHICAL CONSIDERATIONS

In all clinical research, ethical considerations must be made about risks, research quality, and the autonomy and integrity of participants. In essence, the benefits of increased knowledge must be balanced against the possible harm to participants.

Harm can be obvious, such as physical injury after surgery, but also less obvious, such as wasted time and resources on low-quality research. To make matters more complicated, participants may not be able to benefit from the increased knowledge that they help uncover. This is usually the case when performing surgical research, since surgical procedures can rarely be undone. For example, in studies III, IV, and V, the included patients had already undergone surgery and could therefore not use the knowledge from the studies to change their earlier decisions.

Another significant but less obvious ethical aspect is that information in itself can be harmful. For example, in study V, patients were invited for a long-term follow-up with PSG, in which the majority participated. As could be expected, it was revealed that some patients had relapses that they did not know about. From the researcher's point of view, such information is always valuable. However, from the patient's point of view, it is more complicated, especially if they are unwilling to participate in any further treatment. This is not easily explained in advance and highlights the importance of the patient information before surgery.

Autonomy is perhaps the most important ethical consideration, and largely depends on free decisions made by informed adults. All patients in the studies were adults and gave consent to participate after the study was explained verbally and in writing. Furthermore, there was no economic reimbursement involved that could put participants in a position of dependence. On the other hand, in accordance with study protocol, participants were given priority in the surgery queue over other patients. This could be considered an ethical issue, since it may have affected the patient's decision. However, the study participants could at any time withdraw their consent and return to ordinary treatments protocols without any explanation or questions asked. Overall, autonomy also stresses the importance of accurate and easily understood patient information.

Regarding personal integrity, all data was anonymized without any possibility of identifying specific patients and should not pose any risk of personal harm. All of the data was kept inaccessible to unauthorized persons.

In summary, the assumed benefits of the studies were judged to outbalance any risks.

### **3.8.1 Approvals from ethical review boards**

All participants were adults and gave informed consent to participate. The Regional Ethics Committee (diary number 2007/449-31/3) initially rejected **study III**, since it was viewed as unethical to keep the control group on delayed surgery for six months. However, when it was clarified that the normal waiting time for surgical treatment was more than six months and that the control group was without any treatment before inclusion, the study was authorized by the Central Ethics Committee (diary number Ö21-2007). No application was made for the ethical approval of **study I**, since there was no risk of physical or psychological harm.

The diary numbers for **study II** was 2016/331-32 and 2015/755-31/2, the diary numbers for **study IV** was 2007/449-31/3 and Ö 21-2007, and the diary numbers for **study IV** was 2018/214-32.

## 4 RESULTS

### 4.1 STUDY I AND STUDY II – THE FRIEDMAN STAGING SYSTEM

All participants completed the studies, and there were no missing values or dropouts. In **Study I**, 15 doctors participated and examined each other, resulting in a total of 210 examinations. Since they did not rate themselves and the kappa was calculated for each pair of raters, there were 13 subjects for each pair of raters. This amounted to 105 comparable kappa coefficients.

In **Study II**, 14 doctors examined the tonsil size, Friedman tongue position, and Friedman stage of 12 patients with OSA, which resulted in a total of 168 examinations and 91 comparable kappa coefficients. No patient had a BMI of over 40 kg/m<sup>2</sup>, and BMI did not affect the staging (since BMI>40 automatically gives Friedman stage III). Results from both studies are presented in Table 6, with suggested levels of interpretations.

**Table 6.** Results from studies I and II with median Cohen's kappa values for the Friedman tongue position, tonsil size, and Friedman stage.

	Cohen's kappa (first and third quartiles)	Range	Agreement (Byrt)	Agreement (Altman)
Study I (n = 105)				
Tongue position	0.36 (0.23, 0.42)	0.03 to 0.69	Slight	Fair
Study II (n = 91)				
Tongue position	0.32 (0.21, 0.44)	-0.09 to 0.77	Slight	Fair
Tonsil size	0.62 (0.50, 0.63)	0.14 to 1.00	Good	Good
Friedman Stage	0.38 (0.24, 0.55)	-0.08 to 0.86	Slight	Fair

*Note.* Data is shown as the median between the first and third quartiles, range, and corresponding agreement according to Byrt and Altman. Cohen's kappa is between -1 and 1, where 0 represents agreement that would be expected from random chance and 1 represents perfect agreement. Negative values represent agreement that is less than would be expected from random chance alone. "N" represents the number of kappa coefficients.

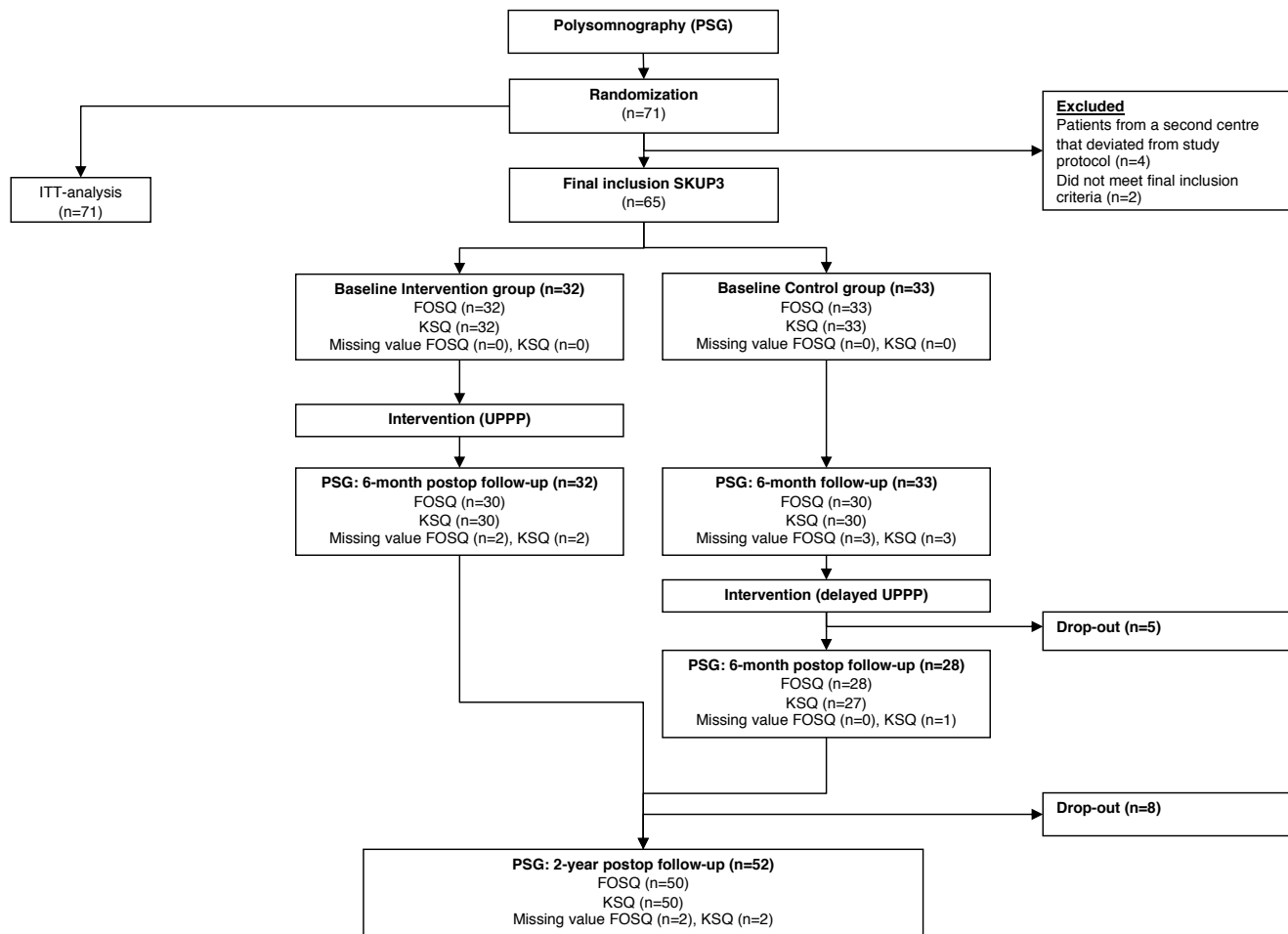
For some patients, the doctors rated the tongue position using both the lowest and highest possible values—an example of very poor agreement. All of the data related to ratings of Friedman tongue position in study II are shown in Figure 10.

Patient	a	b	c	d	e	f	g	h	i	j	k	l	m	n	Rate
1	2	3	4	4	4	2	4	2	2	4	3	4	3	4	
2	3	3	3	3	3	2	2	2	2	3	3	3	2	4	
3	2	1	3	2	2	2	1	2	2	2	2	2	2	2	
4	4	4	3	3	4	3	4	2	2	4	4	4	3	4	
5	1	1	1	1	1	1	1	1	1	2	1	1	1	1	
6	4	1	3	4	4	2	3	3	3	4	3	4	3	4	
7	2	2	3	4	2	1	3	2	1	2	3	4	2	2	
8	1	1	1	1	2	1	1	1	1	1	1	1	1	2	
9	4	4	4	4	4	3	4	4	4	4	4	4	4	4	
10	4	3	2	1	2	1	4	1	3	1	2	1	1	3	
11	3	4	2	3	3	2	3	2	3	3	3	3	2	3	
12	2	1	1	3	2	1	2	1	1	2	2	2	1	2	

**Figure 10.** All individual ratings of Friedman tongue position in study II. It would appear that patient 9 was relatively easy to rate, with only one deviating rater (rater f). Patient 10, on the other hand, seemed more difficult to rate, as every possible rating was used. Notably, raters e and f rated very differently, with only two identical ratings; their individual kappa was also negative at  $-0.09$ , which corresponds to less inter-examiner agreement than would be expected from random chance.

## 4.2 STUDY III – SLEEP QUALITY AFTER UVULOPALATOPHARYNGOPLASTY

Sixty-five patients were included and randomized to either intervention (n = 32) or control (n = 33). All patients who underwent surgery (n = 65) were then followed as a cohort after six months and two years. A flowchart showing dropouts and missing values is provided in Figure 11. All subscales must be missing in a scale for them to be classified as missing values; therefore, the numbers may differ in the flowchart compared to tables.



**Figure 11.** Flowchart of participants in the RCT and all patients who underwent surgery. “N” refers to the number of patients who completed at least one subscale, “FOSQ” refers to Functional Outcome of Sleep Questionnaire, “UPPP” refers to uvulopalatopharyngoplasty, “KSQ” refers to Karolinska Sleep Questionnaire, and “ITT” refers to intention-to-treat.

There were six women in the study and three patients (Friedman stage I and BMI < 30 kg/m<sup>2</sup>) who had not failed non-surgical treatment before inclusion. Baseline characteristics are shown in Table 8. There were no significant group differences, except for the subscale of intimate relationships in the FOSQ.

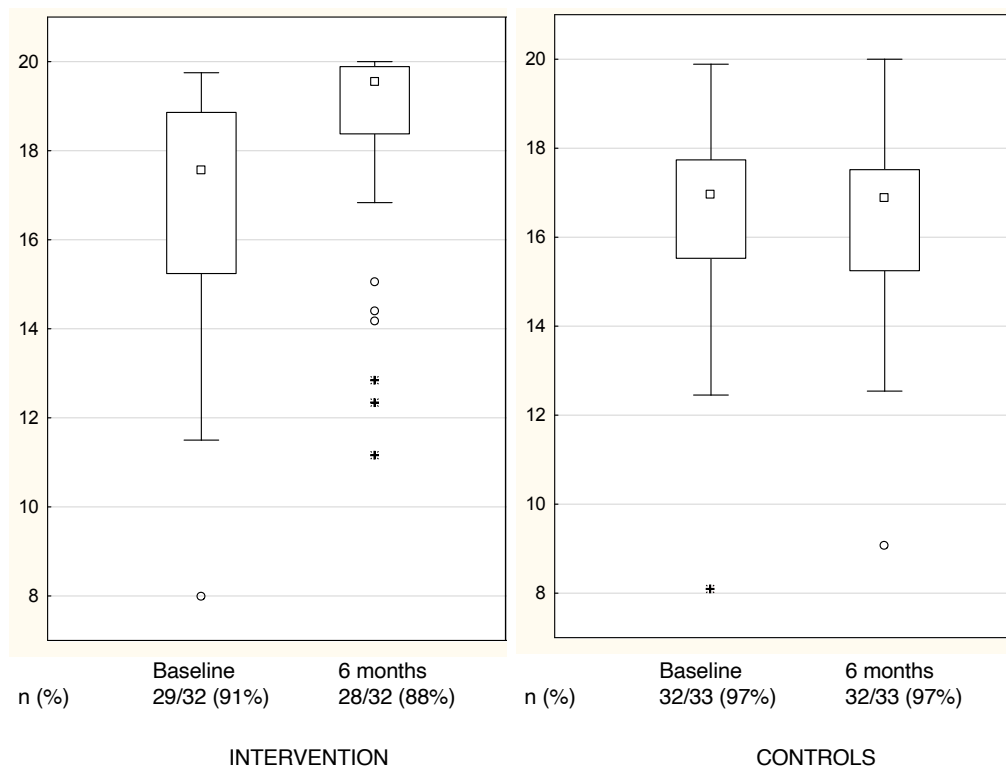
#### 4.2.1 Part 1 – Randomized controlled trial

The rate of missing values was 6% in the FOSQ (range: 0–19%) and 20.5% in the KSQ (range: 3–38%). There were significant improvements in all subscales (except for social outcome in the FOSQ) in favor of intervention. Results are shown with mean values in Table 9 and with boxplots in Figure 12. Results with median values are available in paper III. The intention-to-treat (ITT) analysis (n = 71) did not change the level of significance in any of the subscales.

**Table 8.** Baseline characteristics of participants in the randomized controlled trial

	n	Intervention group (n = 32)	n	Control group (n = 33)	p
Age	32	41.5 (11.5)	33	42.9 (11.7)	0.316
Body mass index (kg/m <sup>2</sup> )	32	28.2 (2.9)	33	27.7 (3.3)	0.519
Epworth Sleepiness Scale	32	12.5 (3.2)	33	12.9 (3.1)	0.519
Apnea/hypopnea index (events/h sleep)	32	53.3 (19.7)	33	52.6 (21.7)	0.901
Sleep latency (vigilance test; min)	27	31 (11.1)	29	34 (9.0)	0.279
<i>Functional Outcome of Sleep Questionnaire</i>					
General productivity	32	3.5 (0.5)	33	3.5 (0.4)	0.571
Social outcome	32	3.6 (0.6)	33	3.6 (0.7)	0.295
Activity level	32	3.0 (0.7)	33	3.0 (0.6)	0.871
Vigilance	32	3.1 (0.6)	33	3.2 (0.7)	0.453
Intimate relationships	29	3.4 (0.8)	32	3.0 (0.8)	<b>0.034</b>
Total score	29	16.8 (2.8)	32	16.4 (2.4)	0.198
<i>Karolinska Sleep Questionnaire</i>					
Insomnia	27	16.2 (6.2)	31	17.2 (6.3)	0.631
Apnea	28	10.8 (4.4)	26	11.0 (3.8)	0.817
Sleepiness	32	12.4 (5.0)	33	13.0 (5.2)	0.701

*Note.* Significant p-values ( $p < .05$ ) are shown in bold. The data shows mean and standard deviation. P-values were calculated with the Mann-Whitney U test except for AHI, BMI, sleep latency, and age, which were calculated with t-tests



**Figure 12.** Total score from the Functional Outcome of Sleep Questionnaire at baseline and after six months in the intervention and control group from independent samples between-group comparisons ( $p < 0.001$ ) (Mann–Whitney U), “n” refers to the number of patients.



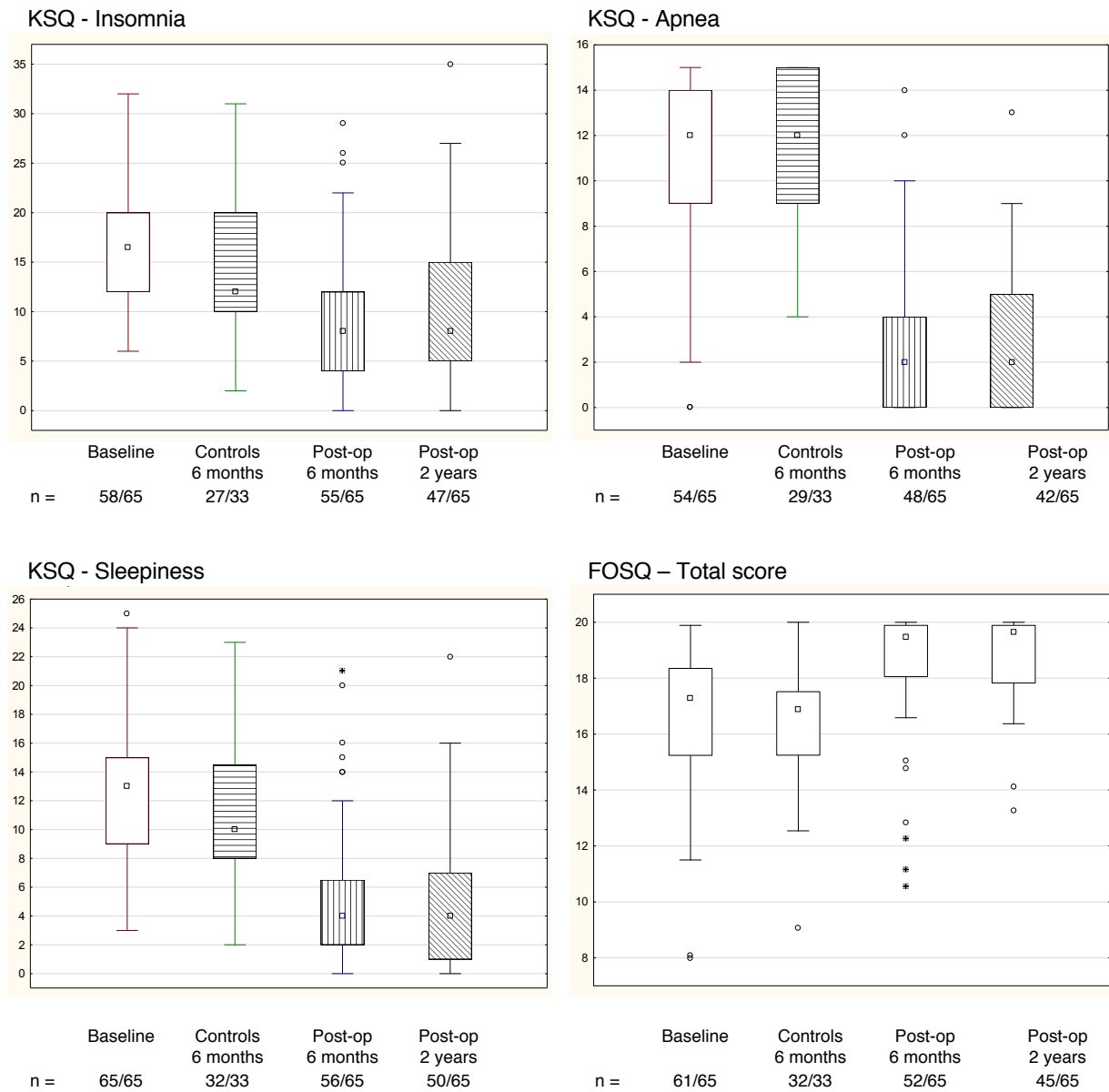
**Table 9.** Results of the RCT from the FOSQ (five subscales and total) and the KSQ (three subscales), with mean difference within groups and comparisons between groups

	Intervention group (n = 32)	Within-group difference	Control group (n = 33)	Within-group difference	Between-group comparisons
	n (mv%)		n (mv%)		p
<b>FOSQ</b>					
General productivity	30 (6%)	0.25 (0.49)	33 (0%)	-0.04 (0.32)	<b>&lt; 0.010</b>
Social outcome	30 (6%)	0.13 (0.47)	33 (0%)	-0.02 (0.61)	0.627
Activity level	30 (6%)	0.47 (0.55)	33 (0%)	-0.08 (0.36)	<b>&lt; 0.001</b>
Vigilance	30 (6%)	0.48 (0.65)	33 (0%)	-0.04 (0.52)	<b>&lt; 0.001</b>
Intimate relations	26 (19%)	0.38 (0.54)	31 (6%)	-0.06 (0.5)	<b>&lt; 0.050</b>
Total FOSQ	26 (19%)	1.53 (2.64)	31 (6%)	-0.20 (1.22)	<b>&lt; 0.001</b>
<b>KSQ</b>					
Insomnia	25 (22%)	-6.1 (6.1)	25 (24%)	-2.0 (4.3)	<b>&lt; 0.050</b>
Apnea	20 (38%)	-7.5 (4.9)	24 (27%)	0.7 (2.7)	<b>&lt; 0.001</b>
Sleepiness	29 (9%)	-7.45 (5.3)	32 (3%)	2.0 (3.5)	<b>&lt; 0.001</b>

“N” refers to the number of patients with complete data at baseline and the six-month follow-up, while mv% represents the rate of missing values for each group and subscale. The data shows mean and standard deviation. The p-values are from independent samples between-group comparisons (Mann-Whitney U tests). Significant differences ( $p < .05$ ) are shown in bold.

#### 4.2.2 Part 2 – Post-operative follow-up of all patients

In all patients who underwent surgery in the per-protocol analysis there was a mean rate of missing values of 13% after six months (range: 11–20%) and 25% after 24 months (range: 23–29%) for the FOSQ. Meanwhile, the mean rate of missing values was 18% after six months (range: 14–26%) and 26% after 24 months (range: 23–35%) for the KSQ. There were significant improvements in all subscales except for social outcome in the FOSQ. The improvements persisted in the two-year follow-up. The results are presented as boxplots in Figure 13 and with p-values in Table 10. The non-response analysis for all patients did not show any significant group differences at baseline in the group with missing values at the two-year follow-up compared to the group with values at the two-year follow-up, except for the subscale of social outcome in the FOSQ ( $p = .032$ ).



**Figure 13.** Boxplots with results from the three subscales in the Karolinska Sleep Questionnaire (insomnia, apnea, and sleepiness) and the total score of the Functional Outcome of Sleep Questionnaire (median, 25%, and 75%), bars (10% and 90%), and outliers at baseline (all), six months for controls, and for all participants who were operated on after six and two years. “N” refers to the number of patients in each group. “KSQ” refers to Karolinska Sleep Questionnaire, and “FOSQ” refers to the Functional Outcome of Sleep Questionnaire.

**Table 10.** Results for all patients who underwent surgery from the Functional Outcome of Sleep Questionnaire and the Karolinska Sleep Questionnaire at baseline, six months, and 24 months

	Baseline		Six months		24 months		Comparison between baseline and 6 months	Comparison between baseline and 24 months	Comparison between six months and 24 months
	n	Mean (sd)	n	Mean (sd)	n	Mean (sd)	p	p	p
FOSQ									
General prod.	65	3.5 (0.4)	58	3.8 (0.5)	50	3.8 (0.3)	<b>&lt;0.001</b>	<b>&lt;0.001</b>	0.931
Social outc.	65	3.6 (0.6)	57	3.8 (0.5)	49	3.8 (0.4)	0.098	0.071	0.933
Activity level	65	3.0 (0.6)	58	3.6 (0.5)	50	3.6 (0.5)	<b>&lt;0.001</b>	<b>&lt;0.001</b>	0.812
Vigilance	65	3.2 (0.6)	58	3.6 (0.5)	50	3.7 (0.5)	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.050</b>
Intimate rel.	61	3.2 (0.8)	52	3.7 (0.6)	46	3.7 (0.6)	<b>&lt;0.001</b>	<b>&lt;0.001</b>	0.754
Total FOSQ	61	16.6 (2.6)	52	18.5 (2.3)	45	18.8 (1.6)	<b>&lt;0.001</b>	<b>&lt;0.001</b>	0.658
KSQ									
Insomnia	58	16.8 (6.3)	55	9.5 (6.8)	47	10.1 (7.1)	<b>&lt;0.001</b>	<b>&lt;0.001</b>	0.327
Apnea	54	10.9 (4.1)	48	3.0 (3.5)	42	2.8 (3.0)	<b>&lt;0.001</b>	<b>&lt;0.001</b>	0.200
Sleepiness	65	12.7 (5.1)	56	5.1 (4.8)	50	5.2 (4.9)	<b>&lt;0.001</b>	<b>&lt;0.001</b>	0.748

*Note.* The data shows mean and standard deviation. P-values were derived from Wilcoxon matched pairs test for within-group comparisons. Significant differences ( $p < .05$ ), are shown in bold. “N” refers to number of patients, “FOSQ” refers to Functional Outcome of Sleep Questionnaire, and “KSQ” refers to Karolinska Sleep Questionnaire.

### 4.2.3 Correlations

There were significant correlations between all subscales in the FOSQ, the KSQ, and the ESS. There were also significant correlations between sleep latency (modified Oxford Sleep Resistance Test or OSLER) and all subscales in the KSQ and the FOSQ (except for social outcome). Moreover, AHI was significantly correlated with all subscales in the KSQ but only to general productivity, activity level, and vigilance in the FOSQ—not to the total FOSQ score. All correlations are detailed in Table 11.

**Table 11.** Results from the RCT at the six-month follow-up with correlation tests between sleep latency (modified OSLER), AHI, ESS, and the questionnaires

	Sleep latency	AHI	ESS	Insomnia	Apnea	Sleepiness
FOSQ						
General prod.	<b>0.61</b>	<b>-0.34</b>	<b>-0.70</b>	<b>-0.70</b>	<b>-0.63</b>	<b>-0.72</b>
Social outc.	0.19	-0.01	<b>-0.40</b>	<b>-0.43</b>	<b>-0.35</b>	<b>-0.42</b>
Activity level	<b>0.54</b>	<b>-0.30</b>	<b>-0.73</b>	<b>-0.76</b>	<b>-0.67</b>	<b>-0.73</b>
Vigilance	<b>0.49</b>	<b>-0.26</b>	<b>-0.75</b>	<b>-0.67</b>	<b>-0.48</b>	<b>-0.71</b>
Intimate rel.	<b>0.46</b>	-0.25	<b>-0.71</b>	<b>-0.72</b>	<b>-0.49</b>	<b>-0.65</b>
Total FOSQ	<b>0.50</b>	-0.22	<b>-0.73</b>	<b>-0.78</b>	<b>-0.64</b>	<b>-0.79</b>
KSQ						
Insomnia	<b>-0.36</b>	<b>0.28</b>	<b>0.75</b>		<b>0.66</b>	<b>0.75</b>
Apnea	<b>-0.36</b>	<b>0.65</b>	<b>0.64</b>	<b>0.66</b>		<b>0.76</b>
Sleepiness	<b>-0.32</b>	<b>0.42</b>	<b>0.81</b>	<b>0.75</b>	<b>0.76</b>	

*Note.* The data shows r-values. Significant correlations ( $p < .050$ ) are shown in bold. Data were analyzed with a Spearman ranked order correlation test.

#### 4.3 STUDY IV – SIDE EFFECTS AFTER UVULOPALATO-PHARYNGOPLASTY

The response rate for the questionnaire about side effects and satisfaction with surgery was 80% (52 out of 65 patients) at the six-month follow-up and 74% (48 out of 65 patients) at the 24-month follow-up. Ninety-four percent of patients had at least one post-operative follow-up. Thirty-one percent (15 out of 48) of patients reported side effects at the 24-month follow-up. The mean age in the group with side effects was higher, 52 years (range: 23–66 years), compared to the group without side effects, who had a mean age of 43 years (range: 23–62 years). The groups with and without side effects were significantly different in age ( $p = .006$ ), satisfaction with surgery ( $p = .04$ ), regrets about undergoing surgery ( $p = .03$ ), recommendation of surgery to others ( $p = .002$ ), and reported taste disturbances ( $p = .03$ ). The results of the questionnaire are shown in Table 12.

**Table 12.** Results from the questionnaire, showing the percentage of patients who were satisfied or had complaints after UPPP

	Six months % (n)	24 months % (n)
Satisfied with surgery	96% (49/51)	83% (40/48)
Regretted surgery	4% (2/52)	6% (3/48)
Would recommend surgery	98% (47/48)	92% (44/48)
Taste disturbances	10% (5/52)	4% (2/48)
Side effects	38% (20/52)	31% (15/48)
None (or no response)	4% (2/52)	-
Mild	17% (9/52)	10% (5/48)
Moderate	10% (5/52)	15% (7/48)
Severe	8% (4/52)	6% (3/48)

*Note.* “N” represents the number of patients who responded “yes” divided by the total number of respondents. “UPPP” refers to uvulopalatopharyngoplasty.

#### 4.3.1 Results from telephone interviews

On average, the telephone interviews were conducted nine years after UPPP (range: 7–11 years). Thirteen out of 15 patients who reported side effects and/or regretted undergoing surgery responded. The interviews were five to 10 minutes in duration. Four patients reported being discontent with the surgery; the main reason for this was an insufficient treatment effect on their OSA. Three of these patients had also resumed or begun non-surgical treatment in the form of CPAP (n = 2) and MRD (n = 1). Nine out of 13 patients with side effects still experienced them but to a degree that they described as minor. Four patients reported no side effects. Three patients had swallowing problems, which they described as minor. Two patients still had changes in voice pitch (one lower, one higher). One patient described difficulty in holding a tone while pronouncing “R” following surgery. At the nine-year interview, this had improved. None of the three patients with reported voice disorders considered these to be an issue at the nine-year follow-up. The four patients who were dissatisfied with the surgery concluded that this was “mainly because of lack of surgical effect” and that they required further OSA treatment as a result. An additional patient, who is not shown in the table, regretted undergoing surgery at 24 months but not at six months and reported no side effects at any follow-ups. At the nine-year interview, the patient could not remember having any side effects or regrets. The results from the interviews are summarized in Table 13.

The following is an example of a response from a dissatisfied patient (5). It has been edited and summarized. For context, this patient had severe OSA at baseline and did not improve after surgery. The BMI was 25.3 before surgery and 26 at the two-year follow-up. Age at surgery was 56 years. A polygraph was later performed at another clinic, showing severe OSA.

- I am not happy with doing the surgery, and it didn't cure my OSA. Once or twice every month, food gets stuck in my throat when I am swallowing. It is annoying, although if I swallow water, the problem disappears. I also have a problem with mucus in the morning. It gets stuck behind my nose and I have to blow my nose to get rid of it. I am sure that it began after I had surgery and that it was not there before. And the surgery didn't help. In fact, I am worse off now with even more apneas. I did a polygraphy and it showed that I have severe OSA. I am currently using a CPAP again, and it actually works for me this time. I would not recommend surgery to others.

The following is an example of a response from a satisfied patient (15). It has been edited and summarized. The participant had moderate OSA at baseline and no OSA after surgery. The BMI was 24.2 before surgery and 22.3 at the two-year follow-up. Age at surgery was 48 years old. A PSG was performed eight years after surgery, showing mild OSA.

- I am feeling good and I am satisfied with having surgery. I have no additional treatment for my OSA today and no remaining side effects. I might have gotten some snoring back—my partner says so—but I haven't been tested and I don't have any daytime symptoms as before. Surgery was painful, and swallowing was difficult for half a year before I recovered, but besides that I can't remember any side effects.

**Table 13.** Individual results for all 15 patients that reported side-effects at the 2-year follow-up

Age	BM	ESS at 6 mo.	AHI at 6 mo.	Satisfied at 2 yr.	Regretted surgery at 2 yr.	Recommended surgery at 2 yr.	Taste disturbances at 2 yr.	Degree of side-effects at 2 yr.	Development between 6 mo. to 2 yr.	Side-effects at 2 yr.	Dissatisfied 9 yr. reason	Other OSA treatment at 9 yr.	Side-effects at 9 yr.
1	58	28	15	77	no	no	no	3	+ from 1	Globus	Yes, bad effect OSA	CPAP	Minor swallow disorder
2	45	32	8	24	no	yes	no	3	+ from 2	Dry throat	Yes, bad effect OSA	Weight reduction	Minor dry throat after snoring
3	61	22	3	16	no	yes	yes	3	+ from 2	Voice disorder	No	None	None
4	57	23	6	12	yes	no	no	2	- from 3	Voice disorder	Yes, bad effect OSA	MAD	Minor voice disorder
5	56	26	12	62	no	no	no	2	same 2	Swallow disorder, mucus	Yes, bad effect OSA	CPAP	Minor swallow disorder, mucus in morning
6	65	37	4	2	yes	yes	no	2	same 2	Voice disorder	No	Minor	Minor voice disorder (low pitch)
7	23	32	9	6	yes	yes	yes	2	new from 0	Morning pain	No	None	Minor mucus
8	66	25	9	27	yes	yes	no	2	same	Globus	No	CPAP	Minor globus
9	59	28	3	22	yes	yes	no	2	+ from 1	Globus	No	None	None
10*	54	26	3	37	yes	yes	no	2	- from 3	Gag reflex	-	-	-
11*	40	30	3	51	yes	yes	no	1	new from 0	Dry throat	-	-	-
12	55	31	3	37	yes	yes	no	1	same 1	Swallow dry food	No	None	None
13	39	27	3	29	yes	yes	no	1	same 1	Swallow disorder	No	None	Minor swallow disorder, minor voice disorder (high pitch)
14	48	32	4	17	yes	yes	no	1	same 1	Mucus	No	CPAP	Minor mucus
15	48	22	9	2	yes	yes	no	1	- from 2	Swallow disorder	No	None	None

Note. "BMI" represents body mass. "ESS" refers to Epworth Sleepiness Scale. "AHI" refers to apnea-hypopnea index. Patient no. 10 and 11 did not respond for interview.

#### **4.4 STUDY V – EIGHT-YEAR FOLLOW-UP AFTER UVULOPALATOPHARYNGOPLASTY**

Sixty-five patients were initially included in this study, and the dropout rate gradually increased over the years. At the eight-year follow-up, there were 18 dropouts (28%) for the PSG and 25 missing values for the ESS (38.5%). The ESS was completed at the visit for the PSG. However, since all items needed to be filled out for the ESS to be complete, the number of values available for analysis was lower for the ESS, thus resulting in a higher number of missing values. On average, the follow-up was performed 8.4 years from baseline (range: 6.7–10.6 years).

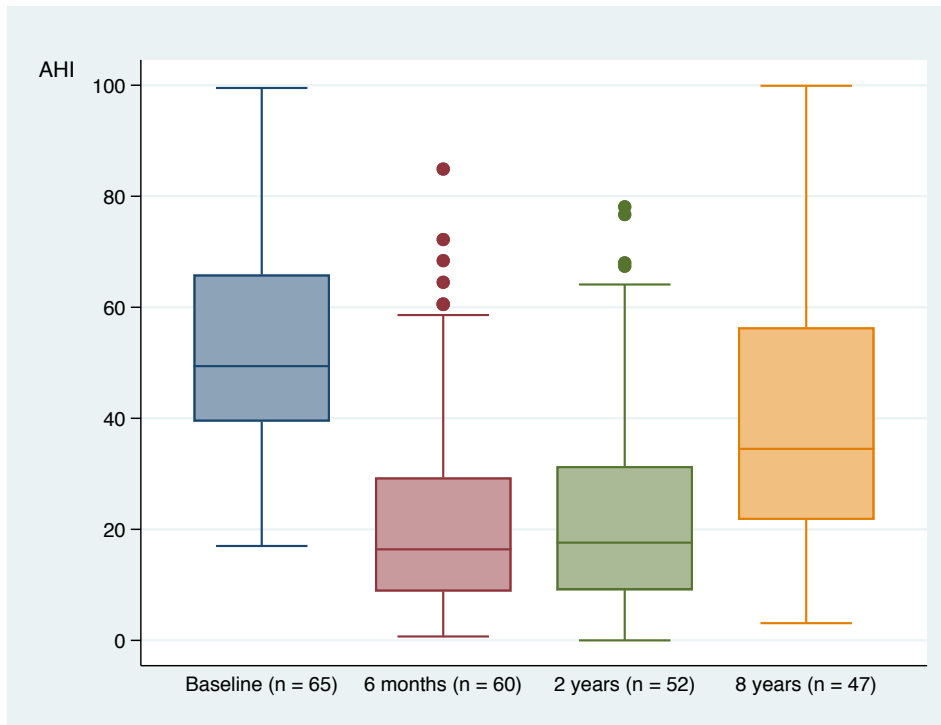
At the eight-year follow-up, AHI was significantly improved compared to baseline, but it had also significantly increased compared to the two-year follow-up. The mean decrease in AHI was 27% or 14 events per hour (52.9 to 38.9,  $p < .001$ ) between baseline and the eight-year follow-up. The mean increase in AHI was 61% or 14.7 events per hour (24.2 to 38.9,  $p < .0001$ ) between the two-year and eight-year follow-ups. The changes in AHI are shown as boxplots in Figure 14.

Daytime sleepiness, as measured through ESS, was significantly improved at the eight-year follow-up compared to baseline and, in contrast to AHI, did not worsen compared to the two-year follow-up. The median improvement in ESS was 54% or 7 points (13 to 6,  $p < .0001$ ). The median increase in ESS between the two-year and eight-year follow-ups was not significant at 20% or 1 point (5 to 6,  $p = .7967$ ). The results for ESS are shown as boxplots in Figure 15.

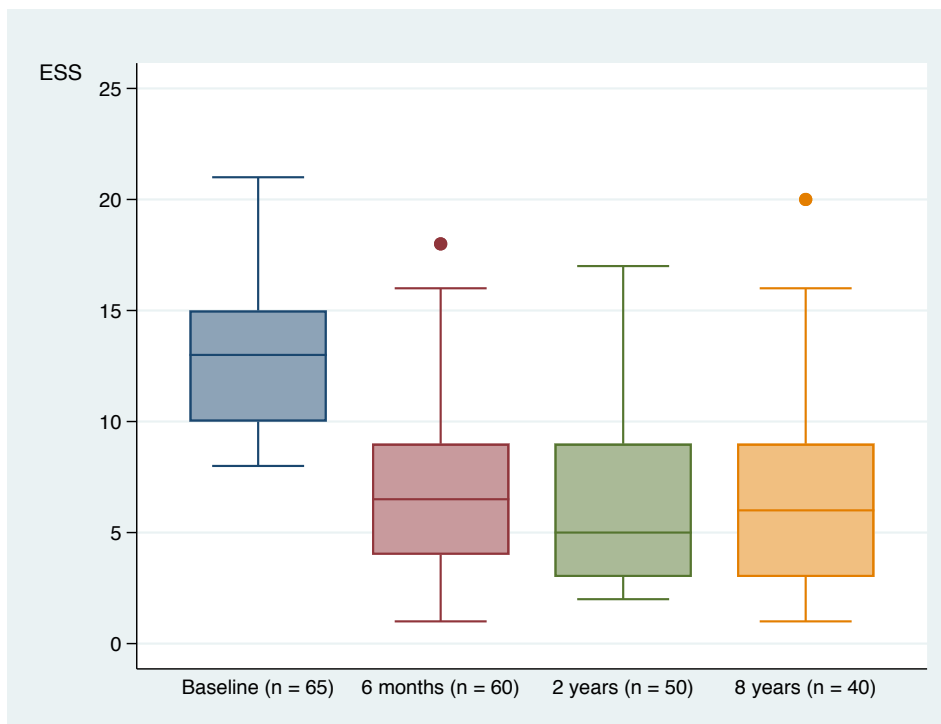
Body mass index significantly increased between baseline and the eight-year follow-up by 1 kg/m<sup>2</sup> (28 to 29 kg/m<sup>2</sup>,  $p < .0001$ ) and between the two-year and eight-year follow-ups by 0.9 kg/m<sup>2</sup> (28.1 to 29 kg/m<sup>2</sup>,  $p = .0024$ ). In contrast, neither AHI or BMI changed in significant numbers between baseline and the two-year follow-up. Figure 16 shows AHI at every follow-up for all patients with complete data at the eight-year follow-up.

To evaluate factors that could predict long-term results, a multiple regression model was constructed. The model showed that BMI at baseline, changes in BMI (between baseline and the eight-year follow-up), and sex were significant factors for long-term results. By contrast, Friedman stage, tongue position, and tonsil size were not significant. Furthermore, AHI at baseline and changes in supine sleeping position between baseline and the eight-year follow-up were not significant. These factors were therefore not included in the final regression model.

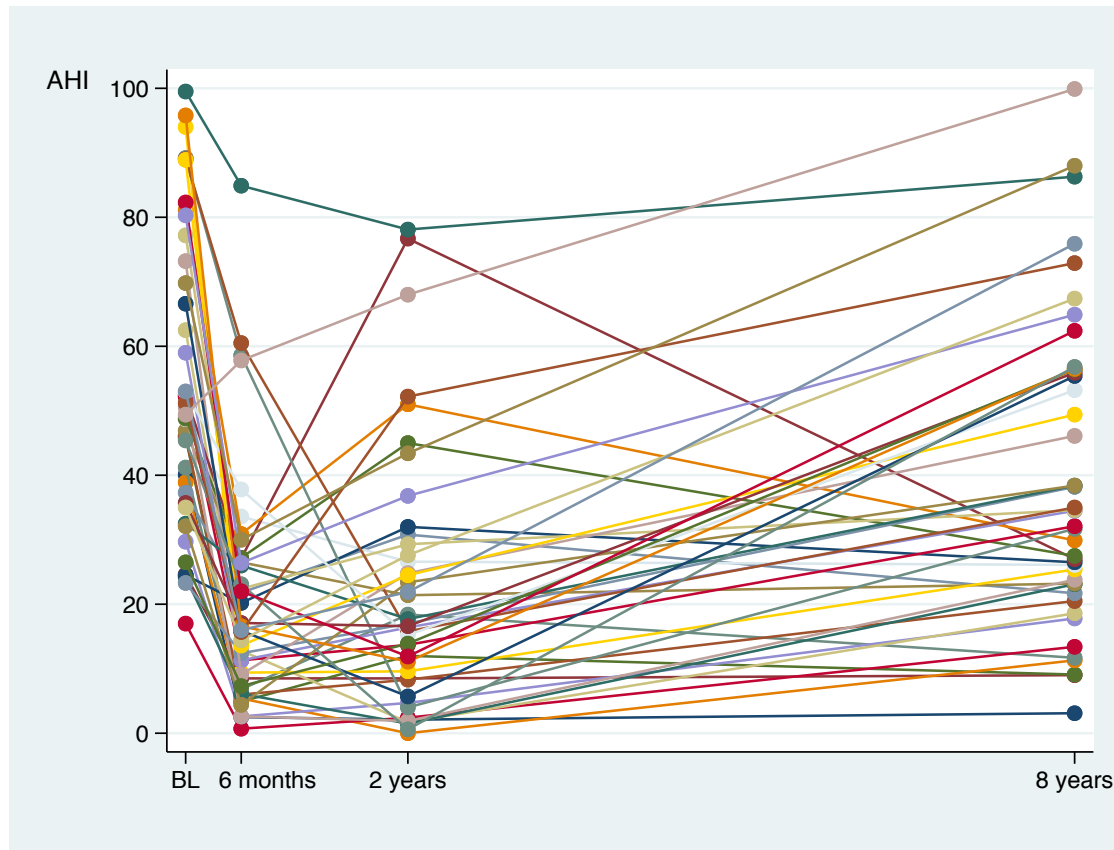




**Figure 14.** Boxplot of apnea-hypopnea index (AHI) values at baseline, six months, two years, and eight years after modified uvulopalatopharyngoplasty for all patients. “N” refers to the number of patients. The boxes represent median (line in each box) and quartile values, the whiskers represent the 1.5 interquartile range, and the dots represent outliers.



**Figure 15.** Boxplots of Epworth Sleepiness Scale (ESS) scores at baseline, six months, two years, and eight years after modified uvulopalatopharyngoplasty for all patients. “N” refers to the number of patients, and “AHI” refers to apnea-hypopnea index. The boxes represent median (line in each box) and quartile values, the whiskers represent the 1.5 interquartile range, and the dots represent outliers.



**Figure 16.** Line graph showing apnea-hypopnea index (AHI) for all patients ( $n = 43$ ) with complete data from every follow-up. “BL” refers to baseline.

The eight-year AHI in the group of patients who were overweight or obese at baseline was 22.9 events per hour higher than the group of patients with normal weight at baseline ( $p = .015$ , 95% CI 8.8–37). In addition, for every 1 kg/m<sup>2</sup> increase in BMI, the eight-year AHI increased by 3.8 events per hour ( $p = .015$ , 95% CI 0.8–6.9). Being male also increased the eight-year AHI by 21.3 events per hour compared to being female ( $p = .043$ , 95% CI 0.67–41.89). Notably, however, there were only four women at the eight-year follow-up.

#### 4.4.1 Dropouts and missing values

The non-response analysis, in which baseline AHI and ESS values for the group without values at the eight-year follow-up were compared with the group with values at the eight-year follow-up, did not reveal any significant differences. In addition, the sensitivity analysis with ITT for all 65 patients at baseline did not change any results at the eight-year follow-up. To further evaluate skewed results due to dropouts, we excluded all patients without complete eight-year data and analyzed the remaining 47 patients separately. The results, which are presented in detail and with boxplots in paper V, were similar and did not change any overall conclusions.

## 5 DISCUSSION

### 5.1 STUDY I AND II – THE FRIEDMAN STAGING SYSTEM

The main findings in studies I and II were that, due to poor inter-examiner agreement ( $\kappa = 0.38$ ), the Friedman staging system may be an unreliable tool for patient selection for UPPP. This aligned with the beforehand hypothesis and experience from clinical practice. It was illustrative that some patients were staged as both Friedman stage I and Friedman stage III—the highest and lowest possible values. At our clinic, patients staged as Friedman I are usually offered surgery, while patients staged as Friedman III are not.

Inter-examiner agreement on tonsil size was better than that of tongue position. This seems reasonable, since the tonsils are less mobile than the tongue. During the studies, we noted that the relative position of the tongue and soft palate vary according to whether the patient breathes through the nose or through the mouth. During nasal breathing, given that the mouth is open, the soft palate and tongue approach each other (thus favoring the nasal flow of air). During oral breathing, the opposite is true, as shown in previous physiological studies.<sup>133</sup> In both Friedman's original work in 2002<sup>134</sup> and its 2017 update,<sup>135</sup> how patients should breathe is unspecified. This fact may contribute to the poor agreement. We believe that this is a weakness with the system.

In SKUP3, the Friedman stage did not significantly affect success. This could either be explained through poor correlation with surgical success or poor inter-examiner agreement at inclusion. On the other hand, SKUP3 was not powered for a subgroup analysis of surgical success in relation to Friedman stage.

#### 5.1.1 Strengths and limitations

Our results contradict the original study, which demonstrated very good agreement with a  $\kappa$  of 0.82 among 126 raters who rated 26 videoclips of different tongue positions.<sup>126</sup> Although that study has merit, there is an advantage to examining real subjects in a clinical setting, in comparison with video clips. For example, video clips would not capture variations within the same subject at different examinations.

There were several important limitations. First, though all doctors were instructed in the use of the Friedman staging system, their experiences varied, and only two were strictly subspecialized in sleep medicine. This may result in false low agreements compared to what a more specialized unit would achieve. One way to evaluate this could be to divide the group into categories after experience. However, since there were only two sleep specialists in the study there would only be one comparable pair of raters. Therefore, a subgroup analysis was not considered to be of value.

Secondly, Cohen's kappa statistic does not differentiate between exactly how wrong a scoring is. Therefore, it is regarded as equally wrong if two doctors rate 1 and 2 or 1 and 4. This could be statistically adjusted for with a weighted kappa, but since the data was ordinal, with only a few different values to choose from, and the studies that we compared with did not make this adjustment, we decided to use non-weighted kappa statistics.

Critically, and as discussed in detail in a previous section (section 1.5.3), there are still no suitable alternatives for the Friedman staging system to predict surgical outcomes. Until then, the Friedman staging system may be the best alternative; that said, the system requires an update, with detailed descriptions on how the staging should be performed and a particular focus on patients' breathing.

## **5.2 STUDY III – SLEEP QUALITY AFTER UVULOPALATO-PHARYNGOPLASTY**

In summary, study III demonstrated positive effects of UPPP on subjective sleep quality, as measured through questionnaires (FOSQ and KSQ), compared to the control group. In addition, when evaluating the entire group after surgery, the results were stable over a two-year period, suggesting that the effect may last and may not be caused by placebo. Overall, eight out of nine subscales in the FOSQ and KSQ were improved at six months and 24 months after surgery.

In the RCT, the subscale of vigilance showed the greatest improvement among all subscales. This is of interest, since the subscale includes questions about operating motor vehicles and patients with OSA have a documented increased risk of traffic accidents (see section 1.4.3). Results from this subscale also correlated with the objective vigilance test in the RCT. Interestingly, previous studies involving a driving simulator had suggested that UPPP in patients with severe rhoncopathy (i.e. heavy snorers) may have a beneficial effect on driving performance compared to controls<sup>136</sup> and that the risk of accidents normalized after UPPP.<sup>137</sup> Taken together, these findings may indicate a beneficial effect of UPPP on traffic safety.

The only subscale that did not show any significant group differences in the RCT or the follow-up of all patients who underwent surgery was social outcome. On the other hand, the value for this subscale was high already at baseline; therefore, there was little room for improvement.

The total FOSQ score for all patients who underwent surgery significantly improved from 16.6 to 18.5 and to normal values (> 18) after UPPP. These findings were very similar to

a 2020 RCT that compared UPPP (including tongue base reduction) versus conservative treatment. This study demonstrated an improvement in total FOSQ score from 15.1 to 18.6.

No study has directly compared UPPP with other treatments, but there are other studies that have used the FOSQ. Most of these studies had a similar total score and most to a normal level, but from a lower baseline. For example, Billings et al. analyzed data from 135 patient before and after CPAP treatment and found an improvement in total FOSQ score from a mean score of 14.7 to 18.2.<sup>127</sup> Another example from a study of maxillo-mandibular advancement surgery showed a similar improvement in the total FOSQ score, with an increase from a mean score of 14.1 to 18.3.<sup>138</sup> In addition, a study on hypoglossal nerve stimulation with 126 patients found an improvement in total FOSQ score from 14.3 to 17.3.<sup>103</sup> By contrast, an RCT conducted by Marklund et al. found no significant differences at follow-up in total FOSQ score or KSQ between MRD and a placebo device, though PSG improved.<sup>139</sup> However, all of these comparisons must be made with caution due to different populations and study designs.

### **5.2.1 Strengths and limitations**

The strength of this study is its randomized controlled design and the prospective follow-up of all patients who underwent surgery, as well as the correlations with previous results from the same cohort.

There are, however, several limitations. First, for all interventions, there is the possibility of confounding due to a placebo. This is especially true for patient-reported outcomes, such as the questionnaires used in the present study. Some circumstances, however, do speak in favor of an actual effect. For instance, there were correlations between objective and subjective data in that the questionnaires significantly correlated with sleep latency in the vigilance test and with AHI. These results suggest a real effect of UPPP, though a placebo effect still cannot be excluded. Furthermore, the follow-up after two years did not reveal any signs of decreased effect, and a placebo effect would presumably decline over time. On the other hand, the expected duration of a placebo effect is unclear. A well-known study on arthroscopic knee sham surgery for osteoarthritis demonstrated positive effects two years after the procedure,<sup>140</sup> showing that a placebo effect can indeed be long-lasting. Due to a number of ethical issues, sham surgery was never considered as a possibility for the present study, with patients undergoing surgery in general anesthesia.

There are other limitations to this study besides the placebo effect. For example, the questionnaires were secondary data, and the original study was not primarily powered for these, and the results from the FOSQ or the KSQ were not part of any hypothesis that was

clearly specified in advance. Secondly, with the use of questionnaires, there is the risk of recall bias; in addition, the context of participating in a study may affect participants' responses. Another limitation is the 20% of missing values in the KSQ, which increased to 26% at the 24-month follow-up. On the other hand, the ITT analyses in the RCT did not change the results. A final limitation is that the results cannot be extrapolated to all patients with OSA. There was an underrepresentation of women, and our sample also differed from the general population with OSA; it was younger and less overweight, and patients with Friedman stage III were excluded.

### **5.3 STUDY IV – SIDE EFFECTS AFTER UVULOPALATO-PHARYNGOPLASTY**

The overall finding in study IV was that, in our sample of patients with OSA, the majority were satisfied with UPPP six months and 24 months after surgery (96% and 83%, respectively). However, at the same time, approximately one third reported side effects varying from mild to severe. Among the patients who reported side effects or regretted undergoing surgery at 24 months, a follow-up interview after nine years indicated that these side effects were by then of minor concern to most participants. An interesting finding was that younger patients appeared to tolerate surgery better. There was a mean nine-year age difference between the patients with side effects and those without side-effects.

There are studies that both support and conflict with our findings. The former group includes two studies from our research group. One reported that 88% of 158 patients were satisfied one year after surgery,<sup>141</sup> while the other evaluated 50 patients 15 years after surgery and found that 78% were satisfied.<sup>142</sup> These studies used a similarly conservative variant of UPPP. By contrast, a study by Värendh et al. demonstrated that only 52% of 129 patients were satisfied after undergoing UPPP (as described by Fujita et al.<sup>94</sup>) between 1985 and 1991.<sup>102</sup> The rate of remaining side effects was similar to ours—38%—but the nature of the side effects was different and included nasal regurgitation, which was not reported in our study.

In addition, a meta-analysis from 2009 presented an even higher rate of side effects, at 58% (range: 42–62%); the most common were difficulty swallowing and nasal regurgitation (31%).<sup>101</sup> However, comparisons are difficult, since the patients in the studies were subjected to different methods of more or less invasive character, with warm (laser) or cold steel technique.

In the present study, satisfaction with surgery did not correlate with side effects but with AHI. The explanation could be that a majority of patients accepted the side effects if they experienced a significant improvement in their OSA. This could be a confounder between

our findings and those of other studies. The patients in our study were strictly selected according to Friedman stage and BMI, perhaps resulting in a greater likelihood of successful surgery than in other studies. Consequently, this may have led to a greater number of satisfied patients, regardless of side effects.

### **5.3.1 Strengths and limitations**

The strength of this study is the well-defined cohort of patients who underwent several follow-ups. Another strength is the long-term follow-up at nine years; during the telephone interview, the patients could verbalize their post-operative symptoms in detail without being restricted by a questionnaire.

There are also important limitations to this study. The main limitation is the small study sample, making any results vulnerable to chance. This is even more important when evaluating effects that are presumably rare, such as severe complications, which can then go undiscovered. Another weakness is that the questionnaire was not validated, and the concept of minor, intermediate, and severe side effects was subjective. Questions about “inconveniences after surgery” were also included as side effects, though, linguistically, an inconvenience is for most people not understood as being equal to a side effect.

Another limitation is that we only contacted patients who reported side effects or regrets at the 24-month follow-up, and side effects occurring after that time were possibly missed. In addition, three patients reported side effects at six months but had dropped out by the 24-month follow-up and were therefore not included in the telephone interviews. However, all of them reported being satisfied at six months, did not regret the surgery, and would recommend it to others. This may indicate that the side effect that they reported was not of major concern.

Finally, there is the possibility that patients, when personally contacted by telephone, may feel obliged to downsize the severity of their side effects. Similarly, the interviewer could have been unknowingly biased in any direction.

## **5.4 STUDY V – EIGHT-YEAR FOLLOW-UP AFTER UVULOPALATO-PHARYNGOPLASTY**

The overall finding in this study was that the effect of UPPP declined over time but remain improved compared to before the surgery. Daytime sleepiness (as measured through ESS), on the other hand, remained improved eight years after surgery. Baseline BMI and the increase in BMI over time seemed to be predictors of poor long-term outcomes. It is

also evident when examining the line graph in Figure 16 that it is very difficult to predict results on an individual level.

Previous research generally supports our results, with an increasing AHI over time after UPPP. For example, a recent meta-analysis demonstrated a mean long-term increase in AHI, with 12 events per hour between the short-term (three to 12 months) and long-term (> 34 months) follow-ups. Meanwhile, overall AHI improved from baseline to the long-term follow-up, with 15 events per hour.<sup>143</sup> These results are very similar to ours, with a mean increase in AHI (15 events/h) between the two-year and long-term follow-ups, while the overall AHI improved from baseline to the long-term follow-up (14 events/h). Comparisons between studies are difficult, however, since different variants of UPPP and definitions of “long-term” were used.

Given the rather poor long-term results, it is reasonable to discuss whether surgery is justified. Surgery can be a risk, and highly effective non-surgical treatments such as CPAP are available. A point in favor of surgery is the improved and stable effect of reduced daytime sleepiness and the fact that surgery is mainly offered to patients who failed non-surgical treatments.

Interestingly, it has been suggested that, although the prevalence of OSA increases with age, it seems to be less dangerous for older patients, with excess mortality only before the age of 50<sup>144</sup> or, according to another study, the age of 60.<sup>145</sup> Improving OSA during these particularly important years could therefore be beneficial, even if the effect declines over time. In addition, 17% of patients in our sample had mild or no OSA eight years after surgery compared to none before surgery, which demonstrates that one group of patients greatly benefitted even in the very long term. Finally, surgery can, if necessary, be combined with renewed attempts at non-surgical treatments. Surgery in combination with an MRD could be a favorable alternative, as the MRD treats collapse from the tongue. Nevertheless, patients should be thoroughly informed about expected long-term outcomes, risks, and side effects and encouraged to adopt non-surgical alternatives at first.

It is unclear why AHI increases in the long term, but being overweight—the most important risk factor for OSA—is likely to be part of the explanation. This is supported by the fact that there were no significant increases in BMI nor AHI between the follow-up at six months and two years. Instead, the increase in both BMI and AHI began somewhere between two and eight years after UPPP, indicating a correlation. Accordingly, the regression analysis showed that the increase in BMI could account for approximately four events per hour of the eight-year AHI. However, since the AHI increase was 15 events per hour, a rather large increase is left unexplained. One explanation could be the



decreasing effect of surgery. Another explanation could be aging and softening of the pharyngeal tissue, as aging itself is a well-known risk factor for OSA.<sup>59–62</sup> Yet another explanation could be the “heavy snorers' disease,” largely explained by the reaction to long-term traumatic snoring, with local neuropathy<sup>42,43,146</sup> and damaged muscle fibers in the palate.<sup>44</sup>

#### **5.4.1 Strengths and limitations**

The main strengths of this study are the use of PSG and a clinically relevant long follow-up time of eight years. Another strength is the well-defined cohort with multiple previous examinations to compare with.

However, there are several limitations to this study, the most important being the drop-out rate. This was somewhat adjusted for with ITT analysis, non-response analysis, and a separate analysis of the group with complete follow-up data. With a very long follow-up, however, the drop-out rate can be expected to increase. Another limitation is the small study population, making subgroup analysis underpowered. Generalization is also difficult, especially with regard to women, since they were only four female participants at the eight-year follow-up, but also with regard to the general population with OSA as a result of our patients being younger and less overweight at baseline. As discussed in detail in Study III (section 5.2.1), the placebo effect might be an issue, mainly with patient-reported data.

## **6 CONCLUSIONS AND CLINICAL IMPLICATIONS**

**Studies I and II:** The inter-examiner agreement of the Friedman staging system was poor, indicating that the system is an uncertain method for selecting patients for uvulopalatopharyngoplasty.

**Study III:** Subjective sleep quality significantly improved six months after modified uvulopalatopharyngoplasty compared to controls. The improvements were stable 24 months after the surgery. The correlations between subjective and objective outcomes and the long-term stability suggested a beneficial effect from surgery, though a placebo effect cannot be excluded.

**Study IV:** A majority of patients with obstructive sleep apnea were satisfied 24 months after surgery, though one third reported experiencing side effects. Younger patients experienced fewer side effects than older patients. Patients with better surgical outcomes were also more satisfied, even if they had side effects. After nine years, the side effects were in general described as minor.

**Study V:** Modified UPPP seems to have effect as a long-term treatment for OSA, though the effect on AHI also significantly decreased over time. Daytime sleepiness, on the other hand, seemed to remain improved even in the long term. A high BMI at baseline and an increase in BMI could predict a decline in long-term results.

**Clinical implication:** Uvulopalatopharyngoplasty can continue to be offered to selected patients with OSA who have failed non-surgical treatments. Patients should be informed that the condition is likely to progress even with surgery. Pre-operative obesity and weight gain after surgery should be avoided. Side effects appeared to be of minor concern in the long term, especially among younger patients. Patient selection remains a challenge.

## 7 FUTURE PERSPECTIVES

Traditionally, surgeons have made decisions based on existing conventions, personal experience, and expert consensus. Although this has merit, surgeons have lagged behind their medical colleagues in terms of evidence-based medicine. Consequently, there is a need for research on new procedures but also finding evidence—or the lack thereof—for existing procedures.

A surgical method that is commonly used as a treatment for OSA is TE alone. In children, this is the standard treatment and is often very effective.<sup>147</sup> In adults, however, TE alone has typically not been considered sleep surgery, probably since the indication in adults is usually chronic tonsillitis or recurrent peritonsillitis. In fact, TE is not mentioned as an option when discussing isolated surgery to treat adult OSA in the 2010 AASM practice guidelines<sup>148</sup> or in a 2020 JAMA review.<sup>149</sup> However, a meta-analysis of 17 studies that evaluated TE alone as a treatment for OSA demonstrated a 65.2% reduction in AHI<sup>112</sup>, similar to the reduction for UPPP in SKUP3.<sup>95</sup> A Swedish study demonstrated that 64% patients with OSA could be completely cured after TE in a prospective intervention study of 28 patients with tonsil sizes 3 or 4. Interestingly, in the subgroup analysis in SKUP3, Browaldh et al. found that surgical results did not differ between patients with tonsil sizes 2, 3, or 4 (results for patients with tonsil size 1 did not significantly improve). Although not powered for that subgroup analysis, this could be an indication that the size of the tonsils is not that important and, conversely, that the pharyngoplasty in UPPP plays an important role. On the other hand, if TE alone was equally effective, it would be preferable since it is a common and easily accessible procedure. At our clinic, there is an ongoing RCT that compares TE and UPPP.

Another future study could be to further investigate swallowing disorders, since difficulty swallowing was a rather common subjective complaint reported in study IV. This could then be objectively evaluated with, for example, contrast medium x-ray.

The patients in SKUP3 were selected to be Friedman stage I or II and excluded if they were stage III (i.e. high tongue and small tonsils). The reason was the poor surgical success rate of only 8% for Friedman stage III, as reported by Friedman et al. in 2002. However, a 2020 RCT, which compared UPPP combined with radiofrequency tongue base reduction with conservative treatment, included all three Friedman stages. The results demonstrated similar improvements in AHI as in SKUP3, when a worse outcome could be expected due to inclusion of Friedman stage III. However, it is plausible that the tongue base reduction plays a more important role if there is not as much tonsil to remove and if the tongue is large. A future RCT could therefore include only patients with Friedman stage III or small tonsils and randomize them to either modified UPPP or modified UPPP in combination with radio frequency tongue base reduction.

Polysomnography is the standard examination for diagnosis and treatment control. As discussed in a previous section (section 1.2.1), this method has its limitations, such as night-to-night variability. However, more importantly, the correlation between PSG and subjective symptoms and daytime sleepiness is weak. This raises the question of whether PSG truly measures what matters to patients. The connection between PSG results and subjective measurements of sleep needs to be better understood.

Patient selection is another area that requires further research. Drug-induced sleep endoscopy<sup>118</sup> is theoretically interesting, but thus far demonstrates weak correlations with actual surgical outcomes.<sup>120121</sup> If introduced in Sweden, DISE would preferably be conducted in the context of a clinical study of surgical outcomes.

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